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Conformationally locked carbocyclic nucleoside analogues

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Konformačně uzamčené analogy karbocyklických nukleosidů.

Dizertační práce

Praha 2012 RNDr. Milan Dejmek

Dedicated to the memory of Prof. Antonín Holý

I solemnly swear that I wrote this thesis myself and that it represents the results of my own work, unless stated otherwise in the text. All books, articles and other sources of information used are properly cited in the References section.

Neither the thesis nor any of its parts have been used previously for obtaining any academic degree.

Milan Dejmek

Abstrakt

Byla vyvinuta metodika přípravy tří typů konformačně uzamčených karbocyklických nukleodisů založených na "bridgehead" substituovaném norbornanovém skeletu - analoga uzamčená v tzv. severní, východní a jižní konformaci. Tyto látky byly připrave-ny na základě strukturní podobnosti s komerčně úspěšným léčivem abacavirem, který je používán k léčbě HIV. Jedním z cílů bylo také studium závislosti antivirové aktivity připravených látek na konformaci jejich pseudocukerné části.

Strategie syntézy spočívala v lineární přípravě vhodného aminového prekurzoru pseudocukerné části a následné výstavbě purinové nebo thyminové nukleobáze na jeho aminoskupině. Syntéza prekurzorů severních a jižních derivátů shodně vychází z 2-karboxymethyl norbornenu a její klíčovou reakcí je Hell-Volhard-Zelinského bromace 2-norbornylkarboxylové kyseliny, která je doprovázena přesmykem bicyklického skeletu. Tím je umožněno zavedení substituentu do tzv. „bridgehead" polohy, místa spojení kruhů. Metodika přípravy východních derivátů je naproti tomu založena na radikálové cyklizaci subsituovaného oximu 4-(brommethyl)-cyklohexanonu, která uzavřením methylenového můstku poskytuje norbornanový intermediát substituovaný v obou bridgehead polohách.

Jako nukleobaze byly při přípravě těchto modifikovaných nukleosidů použity thymin, 6-chlorpurin a 2-amino-6-chlorpurin. Nahrazením atomu chloru v poloze C-6 purinové baze několika nukleofily byla připravena série derivátů s cílem dále zkoumat vztah mezi strukturou látek a jejich biologickou aktivitou.

Jako součást dlouhodobého projektu naší skupiny byly některé z meziproduktů těchto syntéz použity pro přípravu N-9 alkylovaných 6-chlorpurinů. Spolu s deriváty založenými na bicyklo[2.2.2]oktanu a bicyklo[3.2.1]oktanu rozšírily tyto látky naši knihovnu látek aktivních proti Coxsackie viru.

S cílem zjednodušit přípravu cílových látek byly vypracovány nové metodiky pro přípravu jak pseudocukerné části analogů nukleosidů, tak i purinové baze. Diels-Alderova reakce dicyklopentadienu nebo polychlorovaných cyklopentadienů s různými dienofily provedená v mikrovlnném reaktoru výrazně usnadňuje přípravu C-5 substituovaných norbornenů, a nová modifikace Traubeho syntézy purinových nukleobází na aminových substrátech využívající formylované pyrimidinové prekurzory výrazně zvyšuje výtěžky této reakce a při současném zjednodušení jejího provedení.

Abstract

Three novel series of conformationally locked carbocyclic nucleoside analogues based on the bridgehead substituted norbornane bicyclic skeleton were prepared - analogues with the pseudosugar locked in the North, East or South conformation. These compounds were synthesized as structurally related substances to a commercially successful antiviral drug abacavir, which is used in the therapy of HIV. One of the goals was the exploration of the dependence of antiviral activities of prepared compounds on the conformation of their pseudosugar part.

The key intermediates in the syntheses of the North and South analogues, amine precursors suitable for nucleobase construction, were prepared in several steps from easily accessible 2-carboxymethyl norbornene. Introduction of a carboxylic function into the bridgehead position, a key transformation mutual to both syntheses, was accomplished *via* the Hell-Volhard-Zelinsky bromination of norbornane-2-carboxylic acid, which affords rearranged 2-*exo*-bromo-1-carboxynorbornane. Approach to the derivatives locked in the East conformation is based on radical cyclization of substituted 4-(bromomethyl)cyclohexanone oxime, which affords norbornane intermediate substituted in both bridgehead positions.

Thymine, 6-chloropurine and 2-amino-6-chloropurine nucleobases were used in the syntheses of these modified nucleosides and the C-6 chlorine atom of purine bases was subsequently displaced using several nucleophiles in order to build a small library of compounds for the structure-activity relationship study.

As a continuation of one of our group's project, some norbornane-based intermediates from the syntheses of the above mentioned compounds were employed in the preparation of N-9 alkylated 6-chloropurines. Along with derivatives based on bicyclo[2.2.2]octane and bicyclo[3.2.1]octane these compounds expanded our group's library of anti-Coxsackie agents.

In order to facilitate the approach to described compounds, novel procedures for the preparation of both the pseudosugar and the nucleobase part were devised. The microwave-assisted Diels-Alder reaction of dicyclopentadiene or polychlorinated cyclopentadienes with various dienophiles markedly simplified the preparation of C-5 substituted norborenes and the modified Traube synthesis for the construction of variously substituted purine nucleobases on amine precursors led to remarkably higher yields and acceleration of the purine nucleobase introduction.

Acknowledgement

First and foremost I would like to thank to my supervisor, Dr. Hubert Hřebabecký, for his patience, help and guidance during my PhD studies. I am very grateful to the head of our team, Dr. Radim Nencka for his expert advice and for giving me the oportunity to work in his group, and to all members of this team, Dr. Michal Šála, Dr. Martin Kögler, Jaroslava Sklenářová and Veronika Sieberová, and also to members of teams of Dr. Zlatko Janeba, and Dr. Marcela Krečmerová for creating friendly and creative work environment.

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I would like to express my gratitude to Melissa Williams for the language correction and her help with the finalization of this manuscript.

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List of Abbreviations

ABC	abacavir
Ac	acetyl
acac	acetoacetyl
ADA	adenosine deaminase
AdoHcy	S-adenosylhomocysteine
AdoHcyase	S-adenosylhomocysteine hydrolase
AdoMet	S-adenosylmethionine
AIBN	2,2′-azobis(2-methylpropionitrile)
AIDS	acquired immunodeficiency syndrome
AZT	3‘-azidodeoxythymidine
bd	broad doublet
Bn	benzyl
BNA	bridged nucleic acid
Boc	*tert*-butyl carbonate
BOM	benzyloxymethyl
bs	broad singlet
Bu	butyl
BuLi	*n*-butyllitium
Bz	benzoyl
CC_{50}	cytotoxic concentration for 50% cells
COSY	correlation spectroscopy
Cp	cyclopentadiene
*c*Pr	cyclopropyl
CVB	coxsackievirus B
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DDT	dichlorodiphenyltrichloroethane
DEAD	diethyl azodicarboxylate
DHCeA	(1‘*R*,2‘*S*,3‘*R*)-9-(2‘,3‘-dihyroxycyclopenten-1-yl)adenine
DHCaA	(1‘*R*,2‘*S*,3‘*R*)-9-(2‘,3‘-dihyroxycyclopentan-1-yl)adenine

DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*, *N*-diisopropylethylamine, Hünig's base
DMAP	4,4-dimethylaminopyridin
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
EC_{50}	concentration effective for 50% cells
EC_{90}	concentration effective for 90% cells
EI	electron impact ionization
ESI	electronspray ionization
ETV	entecavir
Et	ethyl
FAB	fast atom bombardment ionization
FDA	Food and Drug Administration
GC-MS	gas chromatography coupled with mass spectrometer
HBV	hepatitis-B virus
HCMV	human cytomegalovirus
HHV-8	human herpesvirus type 8
HIV	human immunodeficiency virus
HIV-RT	human immunodeficiency virus's reverse transcriptase
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HSV	herpes simplex virus
i-Pr	isopropyl
LDA	lithiumdiisopropylamide
LNA	locked nucleic acid
m	multiplet
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MCT	methanocarba thymidine
Me	methyl
MMT	monomethoxytrityl
mRNA	messenger RNA
MS	mass spectrometry
Ms	methansulfonyl
MW	microwave irradiation
NMMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl, dimethylpropanoyl
PMB	*para*-methoxybenzyl
PMHS	poly(methylhydrosiloxane)
POP	persistant organic pollutant
q	quartet
RNA	ribonucleic acid
ROESY	rotating frame nuclear Overhauser effect spectroscopy
RSV	respiratory syncytial virus
s	singlet
sept	septet
siRNA	small interfering ribonucleic acid
ssDNA	single stranded deoxyribonucleic acid
ssRNA	single stranded ribonucleic acid
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEA	triethylamine
TEAA	triethylammonium acetate
TEAB	tetraethylammonium bromide
Tf	triflate, trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$TIPDSiCl_2$	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TLC	thin layer chromatography
TMS	tetramethylsilane, trimethylsilyl
tRNA	transfer RNA
Ts	tosyl, toluenesulfonyl
VZV	varicella zoster virus

1. Introduction

1.1. History of nucleic acid components as therapeutic agents

The story of nucleic acid components as potential therapeutics began in the 1940s and through 1950s when their nature and role in cells was established and Watson and Crick described the structure of DNA. Unveiling the principle of the genetic code included in DNA double helix and understanding the mechanisms of metabolic processes involved in the replication of all living organisms led to a simple idea - modifying these keystones of life in a certain fashion might lead to compounds with a potential to interfere with the natural pathways of nucleic acids and thus, if the results of this interference is desireable, possibly give rise to novel drugs.

Early work on nucleoside analogues was aimed at using different, although naturally occurring, sugars connected to one of the traditional nucleobases. cytarabine **1**[1] (araC, FDA approved 1969) is still used in the therapy of acute myeloid leukemia, and vidarabine **2**,[2] apart from being used against myeloid leukemia as well,[2a] (araA, FDA approved 1978) is used as an ophtalmic ointment in the treatment of acute keratoconjunctivis[2b] and against herpes zoster in AIDS patients.[2c]

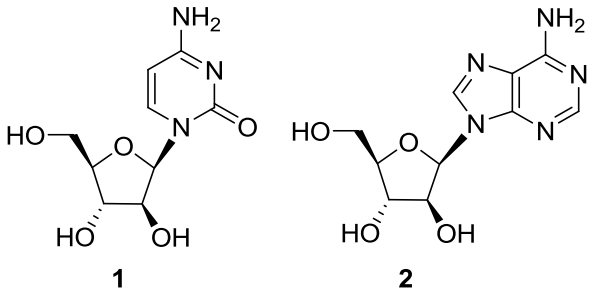


Figure 1. Nucleoside analogues containing arabinose as the sugar part.

Modified nucleobases - substituted purines or pyrimidines not including the carbohydrate part - were also studied and these were the first of nucleic acid components used in clinical practice. 5-Fluorouracil **3**[3] (5-FU, mainly used in the treatment of colorectal carcinoma), thiopurine **4**[4] and thioguanine **5**[4] (used for the treatment of acute leukemias, chronic myelogenous leukemia, inflamatory bowel disease) are good examples of altered nucleobases with antimetabolic properties used in therapeutic practices. Capecitabine **6**[5], a less toxic prodrug of 5-FU, is currently widely used in the treatment of colorectal and breast cancer.

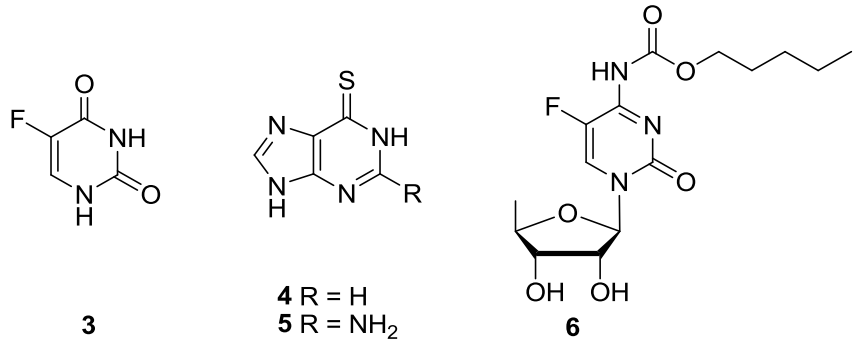


Figure 2. Modified nucleobases used in the clinical practice.

Further development led to structures with sugar, nucleobase or both significantly altered from the natural nucleosides. The oldest antivirotic nucleoside is 5-iodo-2'-deoxyuridine **7**[6] (IUDR) used topically to treat herpes simplex keratitis. Others include thymidine analogue brivudine **8**[7] (BVDU), which is used as antivirotic against herpes zoster and edoxudine **9**[8], which is exceptionally effective against herpes simplex virus (HSV).

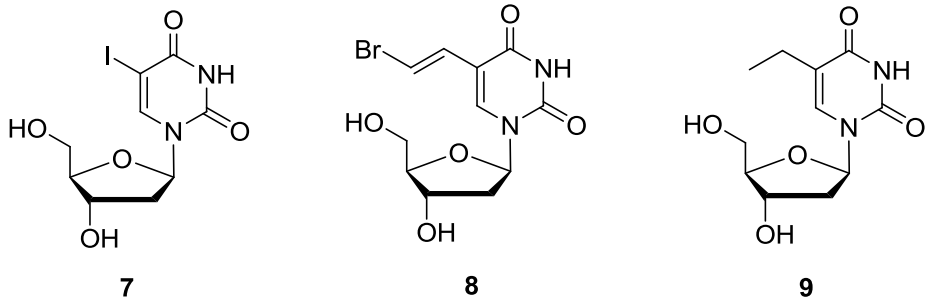


Figure 3. C-5 modified uridines as antiviral agents.

The discovery of acyclovir **10**[9] in 1974 (FDA approved in 1982 for the treatment of HSV infection) led to an extensive work in the field of nucleoside-related medicinal chemistry and following years revealed the tremendous potential of these

compounds as antiviral agents. Modified nucleosides were introduced as an answer to the uprising epidemic of HIV in the 80s[10] - namely zidovudine **11**[11] (AZT, ZDV, first reported in 1964, FDA approved in 1987), didanosine **12**[12] (ddI, first reported in 1964, FDA approved in 1991), zalcitabine **13**[13] (ddC, first reported in 1967, FDA approved in 1992) and lamivudine **14**[14] (3TC, first reported in 1988, FDA approved in 1995 as a combination drug with zidovudine).

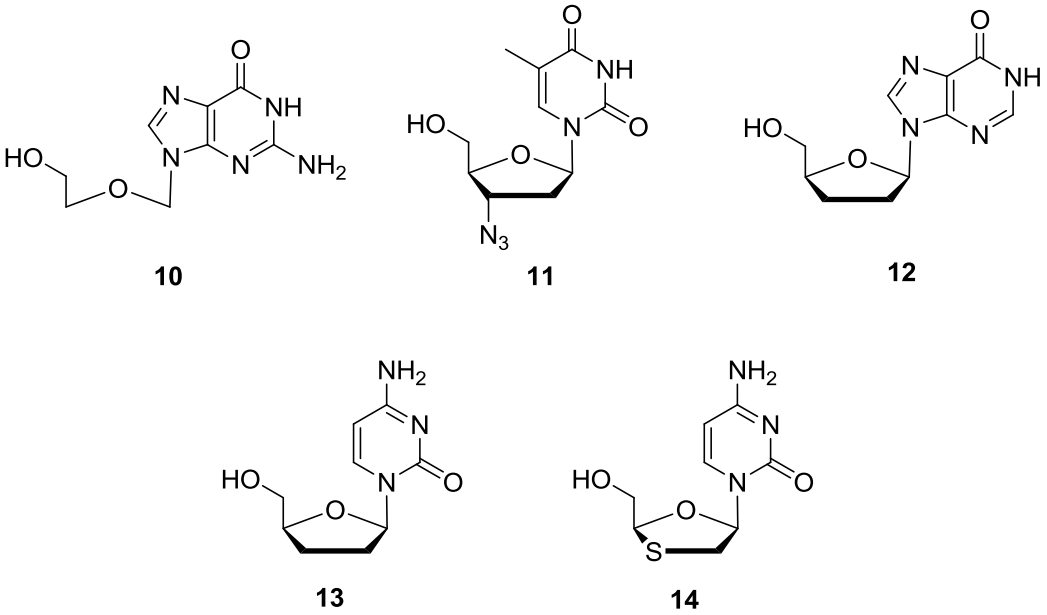


Figure 4. Acyclovir (anti-HSV) and four anti-HIV drugs used in clinical practice.

Applicability of modified nucleosides as antivirals is by far not limited to HSV and HIV therapy. Viruses such as respiratory syncytital virus (RSV) or hepatitis C virus (HCV) are treated with ribavirin **15**[15] (FDA approved in 1980 as an anti-RSV drug and in 1998 as anti-HCV drug to be used in combination with interferon[16]). Also human cytomegalovirus (HCMV - ganciclovir **16**,[17] FDA approved in 1994) and varicela zoster virus (VZV, famciclovir **17**,[18] FDA approved in 1994) are human pathogens treated with nucleoside analogues.

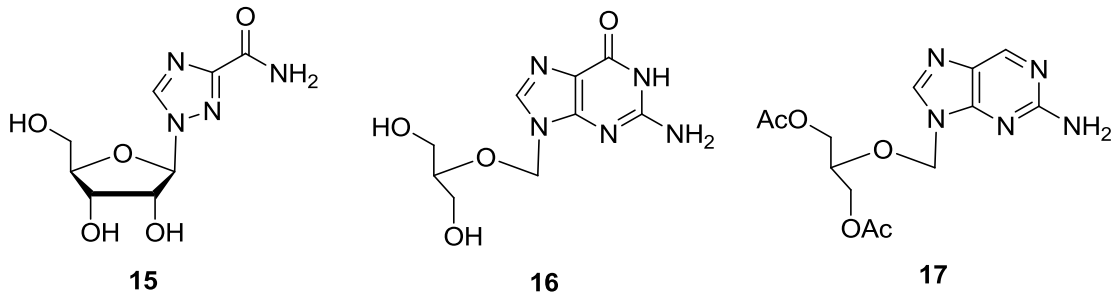


Figure 5. Modified nucleosides used in the treatment of various viral diseases.

Modified nucleosides inhibiting enzyme ribonucleotide reductase (RNR) are clinically used to treat cancer and various forms of leukemia. Fludaribine-5-phosphate **18** is used in the treatment of chronic lymphocytic leukemia[19] and non-Hodgkins lymphomas[20], Gemcitabine **19**[21] is used in the treatment of lung, pancreatic, bladder and breast cancer and Cladribine **20** is approved for the treatment of hairy cell leukemia[22]. Cladribine was also approved for the treatment of multiple sclerosis in Russia and Australia, but after rejection of this drug by the FDA on the basis of insufficient safety data, Merck pharmaceutical company decided to withdraw it from the market completely.[23]

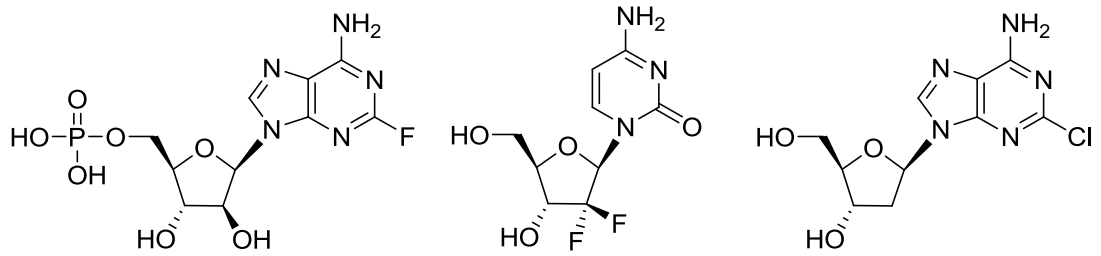
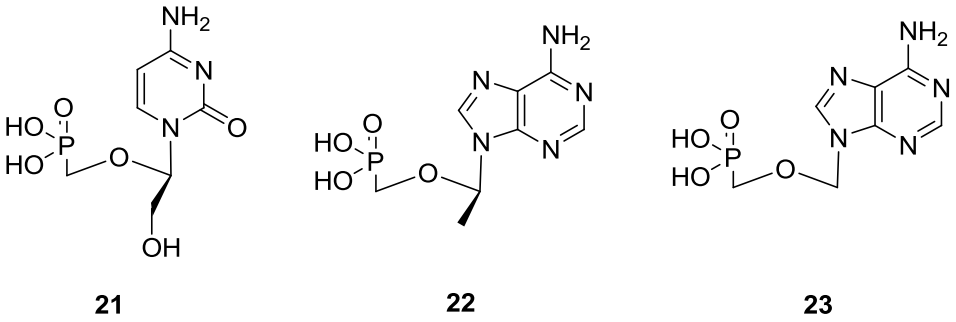


Figure 6. Modified nucleosides inhibiting the RNR enzyme.

A very important class of nucleotide derivatives are nucleoside phosphonates. These compounds are, unlike their parent phosphates, resistant to degradation by cellular nucleolytic enzymes. The discovery of their biological properties by Holý[24] meant a breakthrough in modern antiviral therapy and ultimately led to the success of Gilead Sciences pharmaceutical company. Cidofovir **21**,[25] although being solely approved by the FDA in 1996 for the treatment of HCMV in patients with AIDS, displays a broad spectrum of activity against various DNA viruses.[25b] Tenofovir **22**,[26] nowadays a most widely used nucleoside phosphonate, was approved in 2001 as Viread®, in 2004 as a combinatorial drug Truvada® (with emtricitabine)[27] and in 2006 as combinatorial drug Atripla® (with emtricitabine and efavirenz)[28] for anti-HIV therapy. Viread® was also approved for the treatment of hepatitis B virus[29] (HBV) in 2008 and together with Hepsera® (adefovir[30] **23**, approved 2002) they represent a pillar of HBV therapy.



21 **22** **23**

Figure 7. Acyclic nucleoside phosphonates used in clinical practice.

In the last two decades, a great scientific interest has been paid to oligomers of nucleotides - antisense oligonucleotides,[31] small interfering RNAs[32] (siRNA) and aptamers.[33] The principle behind the therapy with antisense oligonucleotides is the complementary binding of single stranded DNA or RNA sequence to a gene's mRNA and thus silencing this gene. Thus far there is one approved drug, fomivirsen[34] (5'-GCG TTT GCT CTT CTT CTT GCG-3', FDA approved in 1998), which had been used in the treatment of HCMV retinitis, but there is also several drug candidates in various stages of clinical trials (e.g. mipomersen[35] for the treatment of familial hypercholesterolemia, which recently passed phase III; lexgenleucel-T (VRX-494)[36] for the treatment of HIV, which passed phase II or trabedersen[37] for the treatment of highly aggressive tumors, which is currently planned for phase II).

siRNAs are short (20-25 units) double stranded RNAs which interfere with a complementary sequence of a specific gene. Although the use of siRNAs in therapy lies in the distant future, as a proof-of-concept it has been found to be very effective against lethal zaire ebola virus.[38]

Aptamers are oligonucleotide- or peptide-based molecules designed to specifically bind to a target. Pegaptanib[39] (FDA approved in 2004) is an anti-angiogenic aptamer used for the treatment of age-related macular degeneration. Aptamers can also be used for molecular recognition outside the field of clinical medicine.[40]

The main disadvantages of these macromolecules, which cause rather low interest in their development as drugs, include poor bioavailability, difficult transport into cells, stability and tedious preparation.

1.2. Conformationally constrained carbocyclic nucleosides

1.2.1. Strategies for enzymatic stability enhancement

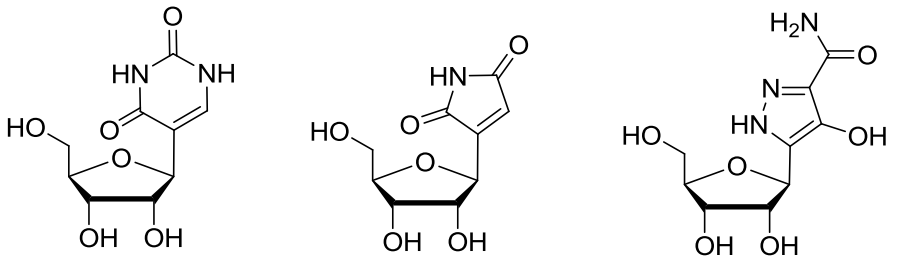
A modern drug must meet certain requirements in order to become approved and successful on the market. In addition to the fundamental imperatives such as high activity, low toxicity and suitable pharmacokinetic profile, there is also the issue of enzymatic stability, which ensures that the compound is not rapidly decomposed by cellular enzymes. The ease of nucleosides' glycosidic bond cleavage by cell phosphorylases is the stumbling block in engeneering nucleoside analogues with better pharmacological properties.

The most widely used methods of increasing nucleosides' stability toward eznymatic degradation are C-nucleosides and carbocyclic nucleosides. In both cases the acidolabile hemiacetal motif[41] is replaced with a more stable cyclic ether and N-alkylated nucleobase, respectively, making these compounds also more chemically stable, as well as mostly preserving the ability to act as substrates for mono- di- and triphosphate formation by cell kinases.

1.2.2. C-nucleosides

C-nucleosides are nucleosides with the heterocyclic and carbohydrate moiety connected with a carbon-carbon bond, which greatly enhances their enzymatic stability.

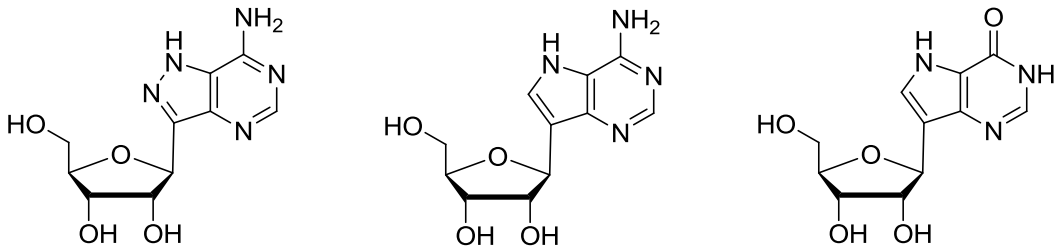
Pseudouridine **24** was identified as the first minor nucleoside present in RNA of eucaryotic organisms (represents cca 4% of all nucleosides in yiest tRNA). It has also been found in beer and was shown to reduce radiation-induced chromosome aberration in human lymphocytes.[42]



24 **25** **26**

Figure 8. Examples of C-nucleosides.

Other important biologically active, naturally occurring C-nucleosides are showdomycin **25**[43] (antibacterial and antitumor activity) and pyrazofurin **26**[44] (broad spectrum of antiviral and antitumor properties). Also direct C-nucleosidic analogues of natural nucleosides were discovered to possess a wide spectrum of interesting biological activities. Formycin A **27**,[45] 8-aza-9-deazaadenosine, has interesting antiviral, antibacterial and antiprotozoal activity. Together with 9-deazaadenosine **28**[46] and 9-deazainosine **29**[47] they possess significant cancerostatic effects.



27 **28** **29**

Figure 9. C-nucleosides with antibacterial and antitumor properties.

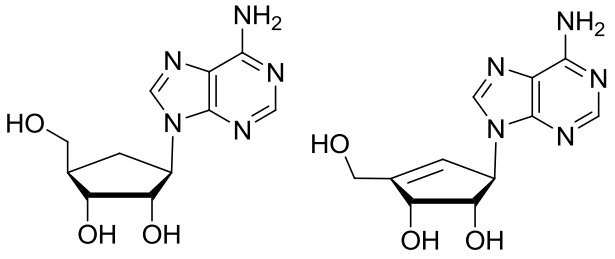
1.2.3. Carbocyclic nucleosides

In carbocyclic nucleosides the oxygen atom of the furanose ring is exchanged for a methylene, ethylene or vinylene moiety. Or, more generally expressed, the carbohydrate is substituted with a cycloalkyl or a cycloalkenyl of various size - from cyclopropyl to cycloxehenyl. From their resemblance to natural nucleosides it is clear that cyclopentane or cyclopentene carbocycles are the most commonly investigated. In addition to the above mentioned increased chemical and enzymatic stability, higher lipophilicity of these compounds has a potential to increase oral efficiency and cell wall penetration.[48]

1.2.3.1. Five-membered carbocyclic nucleosides

Several carbocyclic nucleosides occur in nature. Aristeromycin **30**,[49] carbocyclic analogue of adenosine, was isolated from *Streptomyces citricolor* bacteria and a five-membered family of neplanocines[50] was isolated from a culture of *Ampullariella regularis*. These modified nucleosides gained interest at the forefront of medicinal chemistry, when the biological activity of these compounds was revealed. Aristeromycin was found to possess antibiotic and antineoplastic activity whereas neplanocine A **31**[51] exerted antiviral and cytostatic activity.

Antiviral potency of these compounds is interconnected with their ability to inhibit S-adenosylhomocystein hydrolase[52,53] (AdoHcyase) - the only enzyme known to catalyze the breakage of S-adenosylhomocystein (AdoHcy) to adenosine and homocystein. Since AdoHcy is a competitive inhibitor of S-adenosylmethionine (AdoMet)-dependent methyltransferases, it regulates the most important biological methylation route, which greatly affects other processes, such as mRNA activation of single-stranded (-)RNA. On this rationale a vast synthetic work on derivatives of aristeromycin and neplanocine A was performed in the search for better AdoHcyase inhibitors. Broad spectrum antiviral activity of these inhibitors is remarkable especially towards double-stranded RNA and single-stranded (-)RNA viruses. From DNA viruses they are known to inhibit poxvirus, african swine flu and vaccinia virus.[53]



30 **31**

Figure 10. Naturally occuring carbocyclic nuceosides.

Because the first generation inhibitors were rather cytotoxic due to a number of secondary metabolic effects, the second generation inhibitors were specifically designed to prevent 5'-phosphorylation. Hydroxymethyl group was removed from the skeleton and adenine nucleobase was substituted with 3-deazaadenine. Compounds as DHCeA **32**, DHCaA **34** and their 3-deazaanalogues **33** and **35** were

shown to be AdoHcyase inhibitors with no adenosine deaminase (ADA) or adenosine kinase (AK) activity.[53]

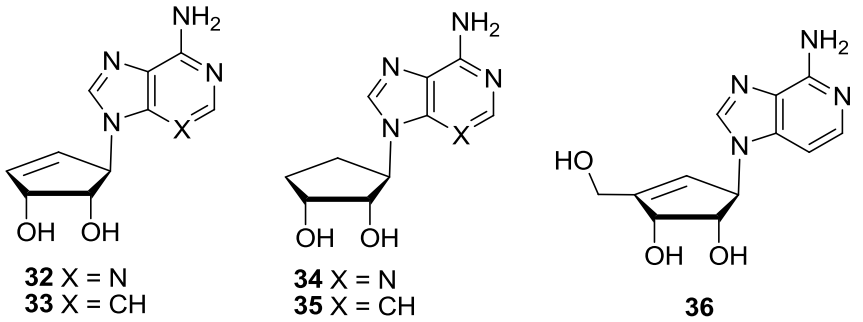


Figure 11. Carbocyclic nucleosides inhibiting AdoHcyase.

AdoHcyase inhibition in human parasites is also feasible. 3-Deazaneplanocin A **36** was found to effectively inhibit growth of *Leishmania donovani*.[53]

In the meantime, among the large number of carbocyclic nucleosides that were synthesized and tested, potent anti-HIV compounds were discovered. Vince *et. al.* in 1988 first described the activity of racemic guanine derivative carbovir **37**[54], which acts as an inhibitor of reverse transcriptase. Due to toxicological and pharmacokinetic deficiencies carbovir had to be eliminated from further development[55], but its prodrug, 6-cyclopropylamino-2-aminopurine derivative abacavir **39**[55,56] (ABC), was approved by the FDA in 1998 for the treatment of HIV. Interestingly, 5'-norcarbovir **38**[57] is approximately equipotent inhibitor of HIV-RT as carbovir.

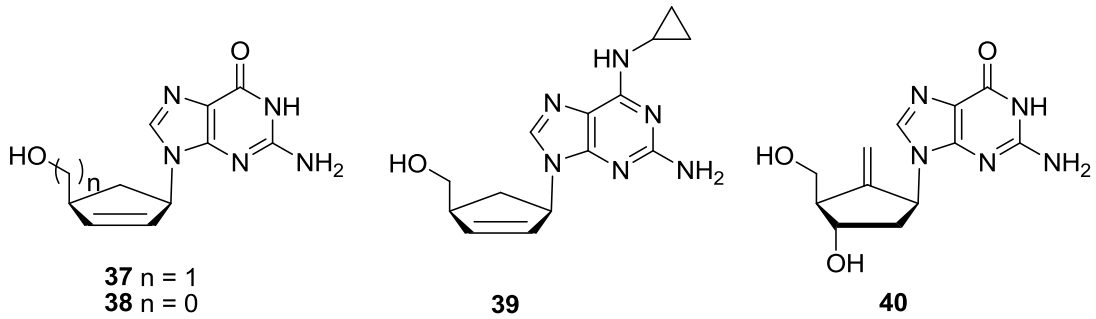


Figure 12. Carbocyclic nucleosides active against HIV and HBV.

Another great success for carbocyclic nucleosides is the approval of entecavir **40**[58] (ETV, 2005) for the treatment of HBV. The activated form of entecavir, entecavir triphosphate, inhibits HBV DNA phosphorylase.[59]

1.2.3.1. Carbocyclic nucleosides with rings of different sizes

There are two important types of three-membered carbanucleosides. First, cyclopropylmethyl analogues were synthesized as conformationally rigid rotamers of carbocyclic derivatives of acyclovir or ganciclovir, but only a few of them exerted good antiviral activity. For example compound A-5021 **41**[60], reported in 1998 by Tsuji *et. al.*, is 20 times more active than acyclovir against HSV-1 and 10 times more active against VZV. Second, carbanucleosides with the nucleobase attached directly to the cyclopropane ring were also synthesized and can be considered contracted derivatives of carbaoxetanocine **43**. However, low or no activity was observed for these analogues.

An interesting structural element was introduced into 3-membered carbanucleosides by the Zemlicka group - compound cyclopropavir **42**,[61] which contains a double bond in the linker between the nucleobase and the cyclopropane ring is very effective against HCMV and Epstein-Barr virus (EBV).[61b]

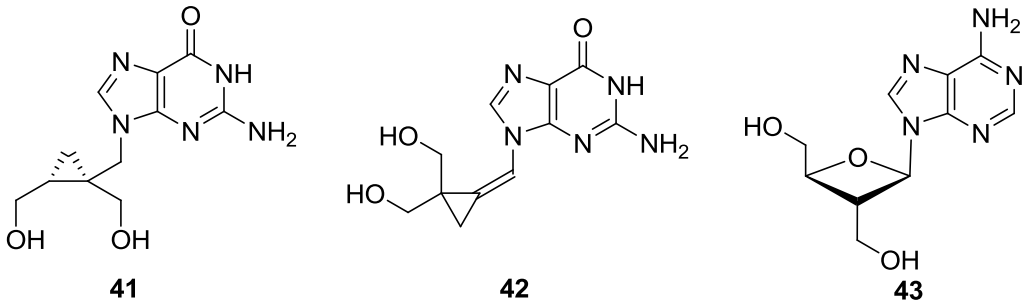
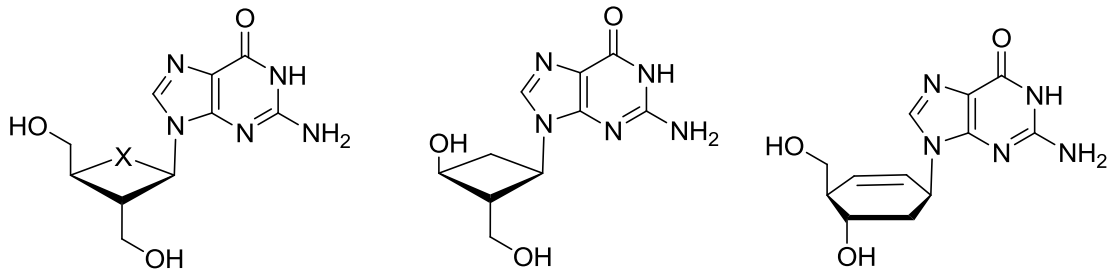


Figure 13. Carbocyclic nucleoside analogues based on cyclopropane ring and oxetanocine A.

Cyclobutane-based analogues are inspired by oxetanocin A **43**,[62] the only known naturally occurring 4-membered ring nucleoside. Oxetanocin A and synthetic oxetanocin G **44** possess good antiviral activity against HIV.[63] One of its carbocyclic derivatives, lobucavir **45**,[64] also known as cyclobut-G, has a very broad-spectrum of activity - it has been shown to inhibit HSV, HCMV, VZV and HIV. Another oxetanocin analogue, 2'-norcarbaoxetanocin G **46**,[63b] exerted antiviral activities similar to acyclovir.



44 X = O
45 X = CH_2

46

47

Figure 14. Oxetanocine G, its two carbocyclic analogues and cyclohexene-based carbocyclic nucleoside.

Majority of work on 6-membered carbanucleosides was done by the Herdewijn group.[65] Their findings strongly implicate that the decisive factor responsible for their biological activity is the pseudosugar conformation. Cyclohexane-based compounds were almost devoid of any antiviral activity, however when cyclohexene-based compounds were evaluated (cyclohexene acts as a bioisostere of the furanose ring), some antiviral activities were found. For example **47**[65c] is similarily active against HSV, VZV and HCMV in comparison with acyclovir and ganciclovir.

1.2.4. Conformational preference of cellular enzymes

The furanose ring of ribose or deoxyribose in solution exists in a series of continuously interconverting conformers. To describe this phenomenon, the concept of "pseudorotation cycle" was introduced,[66] which illustrates a scheme with 20 distinct envelope (E) or twist (T) forms set in a circle according to the main puckering parameter, the endocyclic torsion angle *P*. By convention, the $P = 0$ angle is assigned to C2'-*exo*-C3'-*endo* (T), absolute North conformation and each conformer represents an 18° sector in the pseudorotation cycle. Hence the opposite conformation, C2'-*endo*-C3'-*exo*, ((T), South) is assigned to $P = 180°$.[66]

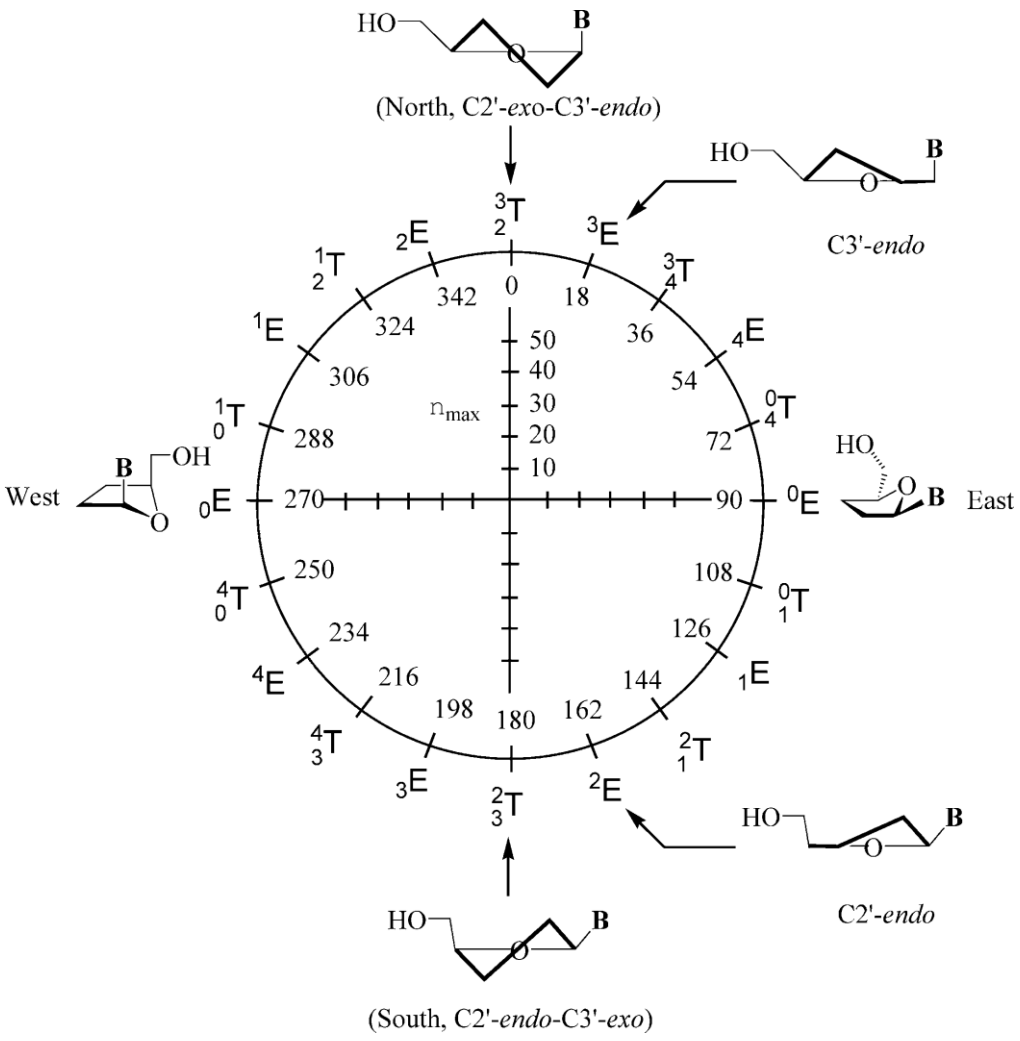


Figure 15.[70a] Pseudorotation cycle depicting furanose conformations.

From the X-ray[66] and NMR[67] data collected on nucleosides, it is apparent that the most common conformations are located in the North (^{3}E, around P = 18°) and South (^{2}E, around P = 162°) regions. Using this information and judging from several known examples of East-conformation nucleosides, we can safely assume that the North-South interconversion proceeds through an Eastern puckering path rather than through the Western.[67]

Conformation of the sugar or pseudosugar part of a nucleoside plays a crucial role in the nucleoside's interaction with cellular enzymes as the active site discriminates between substrates very strictly. It has been shown on the example of AZT[68] and methanocarbathymidines[69] (MCT) **48** and **49** that while a compound in the South conformation (S-MCT **49**) may be a good substrate for phosphorylation by cell kinases, DNA polymerase may exclusively incorporate the North conformer (N-MCT **48**) triphosphate regardless of the elevated S-conformer triphosphate level. The

use of conformationally constrained or locked analogues of nucleosides/tides can therefore be advantageous for the study of a relationship between their conformation and biological activity.[70]

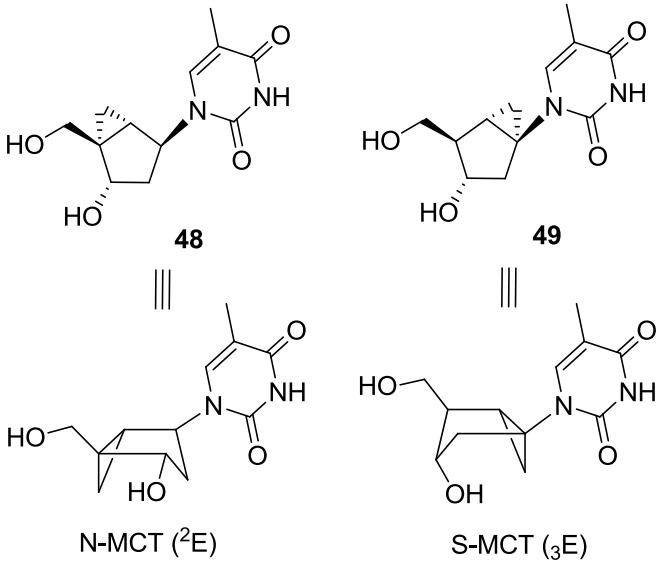


Figure 16. Methanocarbathymidine with conformation locked in two extreme conformations.

An important use of conformationally locked nucleosides was introduced by the discovery of modified oligomeric chains in the second half of 1990s independently by Wengel and Imanishi. These modified oligonucleotides containing one or several of these conformationally locked nucleoside units are called either locked nucleic acids (LNA - Wengel[71]) or bridged nucleic acids (BNA - Imanishi[72]) and possess unique biological properties due to their A-type geometry succesfully mimicking native nucleic acid.[71a,c] In the Figure 17 three different LNA types are depicted.[71a]

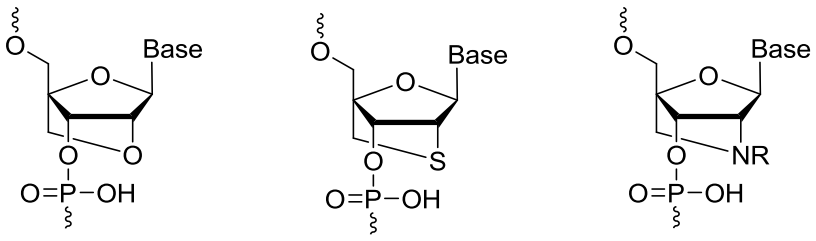


Figure 17. LNA and its modifications containing different heteroatoms.

The hybridization of LNA with DNA or RNA targets led to a remarkable increase of thermal stability (ΔT_m = 1-10°C per LNA monomer).[71a] High affinity hybridization (due to smaller dissociation rate than native DNA) together with mismatch discrimination/selectivity equal or higher to native nucleic acids makes them a versatile tool for ssDNA or ssRNA recognition, such as in diagnostics where they can be used in the detection of genetic code mutations (e.g. detection of factor V Leiden mutation).[73] Danish pharmaceutical company Santris Pharma currently develops an LNA-based anti-HCV drug miravirsen,[74] which is in phase II of clinical trials.

1.3. Synthetic approaches towards carbocyclic nucleosides and their conformationally locked analogues

Synthesis of carbocyclic nucleosides, much like classical nucleosides, consists of two parts - preparation of the pseudosugar hydrocarbon and the introduction of a nucleobase. Synthesis of the pseudosugar is a challenging task, often including a number of reaction steps exploiting the most recent and cutting-edge know-how of organic chemistry. These compounds contain stereogenic center(s), but are usually synthesized as racemic mixtures first and if the racemate exerts an interesting biological activity, enantiomers are either separated or the whole reaction sequence is performed enantioselectively.

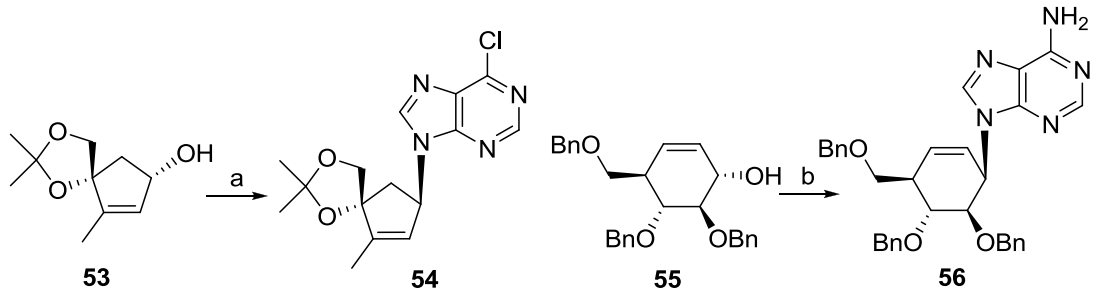
The synthetic strategy of the pseudosugar must always be planned accordingly to the type of reaction intended for the nucleobase introduction. There are several well explored procedures and approaches which afford this transformation and each of them is specific with certain disadvantages.

Below there is a brief review on methods of nucleobase introductions used in the synthesis of carbocyclic nucleosides and some examples of syntheses of either clinically used or otherwise interesting carbocyclic or conformationally locked carbocyclic nucleosides.

1.3.1. Strategies for nucleobase introduction - convergent approach

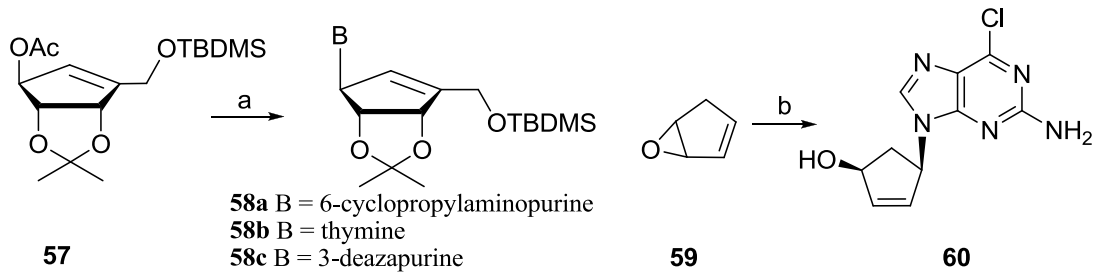
There are several convergent approaches for the introduction of a nucleobase to a carbosugar ring. Despite the fact that they yield the product in one reaction step, they often suffer from certain drawbacks, such as lack of selectivity. Mixtures of N-9 and N-7 isomers may occur in reactions with purine nucleobases and reactions with pyrimidine nucleobases may afford a mixture of N and O isomeric products. Also regioselectivity of the attack with respect to the nucleobase might be a problem. These mixtures are generally difficult to separate and the yields are diminished. The most commonly used convergent approaches are the Mitsunobu reaction and the Tsuji-Trost palladium coupling reaction.

The Mitsunobu reaction[75] involves the activation of a hydroxy group (*in situ* preparation of reactive phosphonium intermediate) by a complex of triaryl- or trialkylphosphine and dialkylazodicarboxylate, allowing direct substitution by a nucleobase with inversion of configuration. Nucleobases react as ambident nucleophiles, which sometimes leads, especially with pyrimidine nucleobases, to the formation of undesired regioisomers (O-alkylation). The Mitsunobu reaction is very popular and well explored, which offers ample oportuniny for its fine-tuning using a wide spectrum of conditions and commercially available reagents.[75d-f] Application of the Mitsunobu reaction include for example the synthesis of abacavir analogue **54** (Douadi *et. al.*)[75b] or introduction of adenine to the molecule **55** (Horváth *et. al.*)[75c]



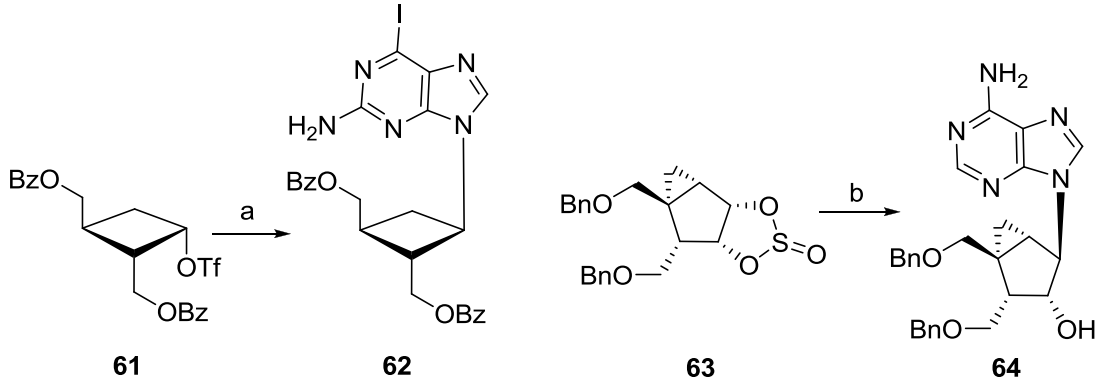
Scheme 1. a) PPh_3, DIAD, 6-chloropurine, DMF; b) PPh_3, DIAD, adenine, dioxane

Palladium(0) catalyzed substitution of allylic esters or carbonates with retention of configuration[76] was pioneered by Trost[76a,b]. The catalyst coordinates to the double bond and forms an η^3 π-allyl complex, which is then attacked by a nucleophile from the less sterically hindered side. Epoxide opening reactions of this type have also been reported. The main drawbacks of this reaction are poor N-9/N-7 selectivity and the possibility of allylic rearrangement. The L- analogue of aristeromycine **58** was synthesized using this reaction by Agrofoglio *et. al.*[76c] and an example of epoxide opening is included in a synthesis of carbovir by Peel *et. al.*[76d] starting from **59**.



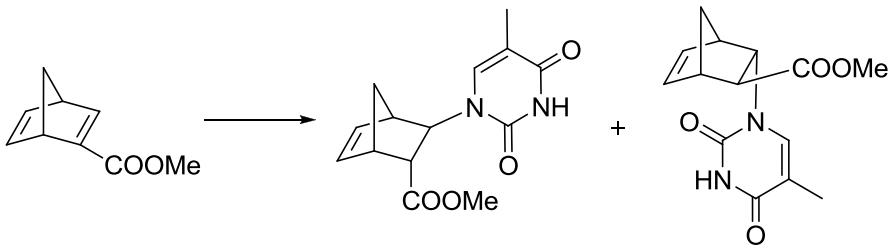
Scheme 2. a) Base, Et_3Al, $Pd(PPh_3)_4$, DMF-THF; b) 2-amino-6-chloropurine, $Pd(PPh_3)_4$, DMSO-THF.

Another popular convergent method in the synthesis of acyclic nucleosides and nucleoside phosphonates, is a simple nucleophilic displacement of halides, mesylates, tosylates or triflates with a suitable nucleobase or also opening of epoxides or a cyclic sulfates in a similar fashion.[77] This reaction proceeds *via* an S_N2 mechanism and has been used for example in the synthesis of Lobucavir derivative **62**[77a] and methanocarbaadenosine analogue **64**.[77b]



Scheme 3. a) (2-amino-6-iodopurine)$^-$-$(Bu_4N)^+$, DCM; b) NaH, adenine, 18-crown-6, DMF.

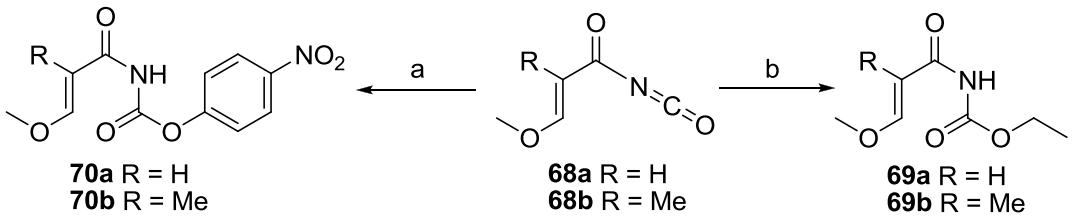
Only limited attention has been paid to Michael addition of a nucleobase to an activated double bond.[78] A handful of examples in the chemistry of carbocyclic nucleosides can be found and mostly pyrimidine-based (uracil or thymine) products, such as isomers **66** and **67**, were prepared in this manner.[78b]



Scheme 4. Thymine, DBU, DMF, **66**:**67** = 7:2 or thymine, K_2CO_3, DMF, **66**:**67** = 2:5.

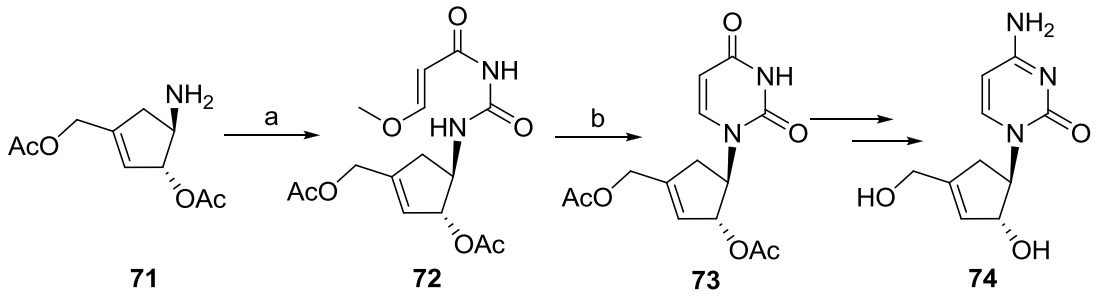
1.3.2. Strategies for nucleobase introduction - nucleobase assembly

Nucleobase assembly on a primary amino group is the most versatile method for the introduction of a nucleobase into the molecule.[79] It consists of two steps - addition of the amine to isocyanate **68** or aminolysis of carbamate **69** and cyclization of the formed acrylourea. The work with isocyanates however, is somewhat inconvenient due to their extreme reactivity (can react with unprotected hydroxy group) and moisture sensitivity, so they are mostly prepared *in situ* right before use.[79a,b]



Scheme 5: a) *p*-nitrophenol; b) EtOH

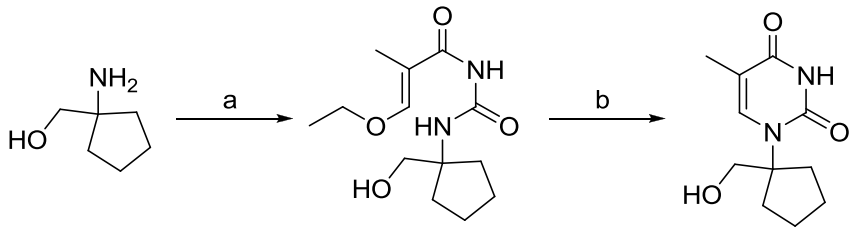
Less reactive carbamate reagents are therefore usually employed, which also provides good functional group tolerance. The pyrimidine ring is subsequently closed under both acidic (diluted organic or mineral acids, Dowex 50 (H^+)) and basic (aquous alkali, ammonia, tertiaty amines) conditions. Currently, the most widely used reagent is ethyl carbamate **69**, which is also used in our research group.[79c,d] A nice example of the preparation of uracil and cytosine analogue of Neplanocine F (**73** and **74**) was reported by Zhang *et. al.*[79e]



71 72 73 74

Scheme 6. a) **68a**, TEA, DCM; b) NH_4OH, MeOH.

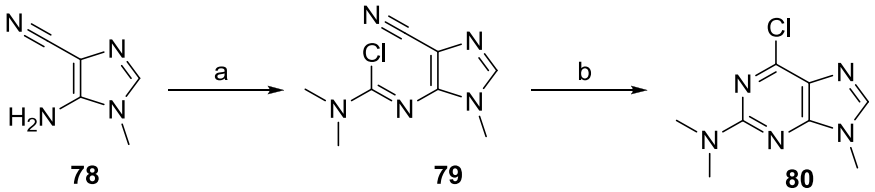
An interesting method was recently devised by Rejman *et. al.*[79f] when authors were trying to find a synthon less reactive and more stable than isocyanate, but more reactive than ethyl carbamate. They discovered that the use of *p*-nitrophenyl carbamates **70** increases yields significantly compared to ethyl carbamate, and these reagents are possible to handle and store under normal conditions. Among many other, synthesis of the thymine derivative **77** is described in their article.



75 76 77

Scheme 7. a) **70b**, dioxane; b) Dowex 50 H^+, dioxane.

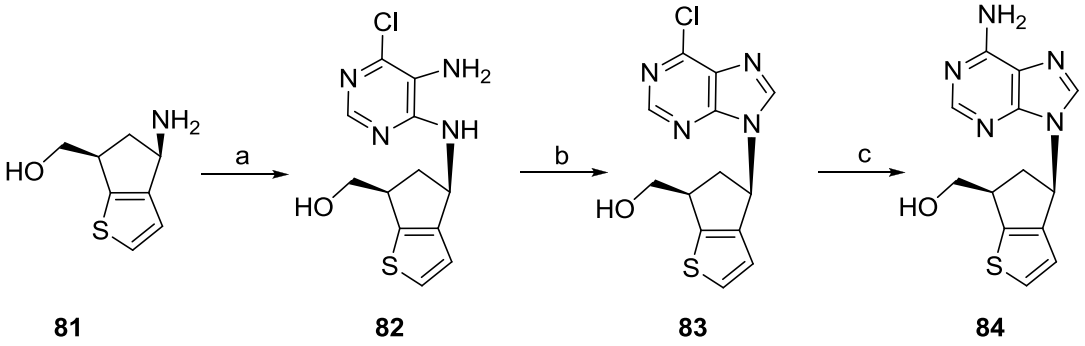
Preparation of the bicyclic purine nucleobase structure can be approached from two sides - either closing a pyrimidine ring on an imidazole intermediate or *vice versa*, closing an imidazole ring on a pyrimidine intermediate. The former, a method used much less frequently, can be explained in the work of Peinador *et. al.*[80] who prepared trisubstituted purine **80** in this fashion. To my knowledge it has never been used in the synthesis of carbocyclic nucleosides.



78 79 80

Scheme 8. a) $Cl_2CN^+Me_2Cl^-$, $Cl(CH_2)_2Cl$; b) HCl, $Cl(CH_2)_2Cl$.

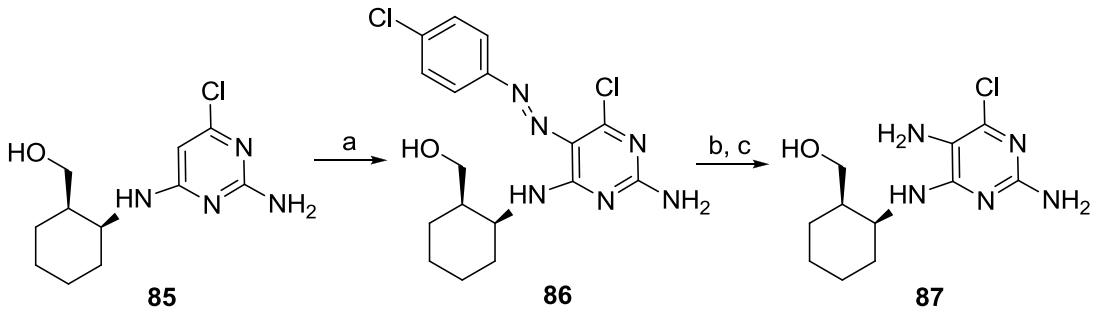
A well explored and widely applicable method is represented by modifications of the Traube synthesis.[81] The aims of this reaction usually include the synthesis of 6-chloropurine or 2-amino-6-chloropurine, which are then easily converted to "natural" or modified nucleobases. In this reaction a suitable pyrimidine synthon is nucleophilically coupled to a substrate containing a primary amine function and the pyrimidine ring is subsequently closed with triethyl orthoformate under acid catalysis. An example of this approach is depicted in Scheme 9, where Abeijón *et. al.*[82] attempted to prepare carbanucleosides with a thiophene ring annulted to the pseudosugar ring (**84**).



81 **82** **83** **84**

Scheme 9. a) 5-Amino-4,6-dichloropyrimidine, TEA, *n*-BuOH; b) $CH(OEt)_3$, HCl; c) NH_4OH, dioxane.

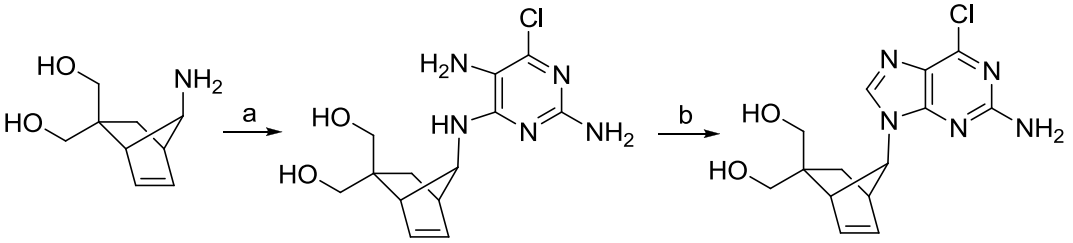
An older and rather obsolete variant of this reaction[83] (Scheme 10) employs a simpler reagent, 4,6-dichloro- or 2-amino-4,6-dichloropyrimidine and, after coupling this species to the pseudosugar moiety, the amino group is introduced to C-5 position of **85** *via* reaction with a diazonium species followed by subsequent zinc reduction. This reaction affords only very modest yields and is nowadays mostly replaced with newer and more sophisticated methods.



85 **86** **87**

Scheme 10.[83c] a) 2-amino-4,6-dichloropyrimidine, TEA, *n*-BuOH; b) *p*-chloroaniline, $NaNO_2$, HCl; c) Zn, AcOH.

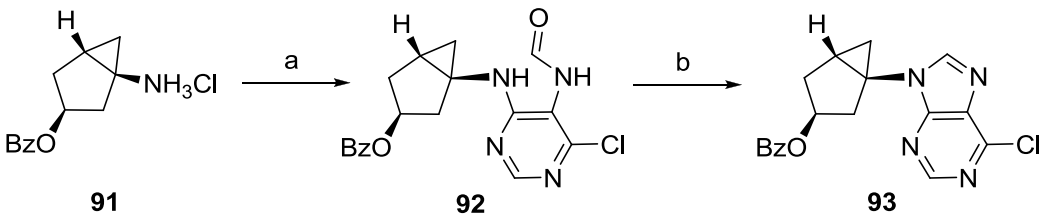
The most utilized modification includes reaction of an amine substrate with 5-amino-4,6-dichloropyrimidine or its 2-amino counterpart and subsequent imidazole ring closure with triethyl orthoformate.[84] This reaction affords reasonable yields, however when more sterically hindered amines are used as substrates, the reaction becomes rather sluggish and yields decrease significantly. In our group this method has recieved a lot of attention and in Scheme 11 Šála *et. al.*[84c] describes the synthesis of conformationally locked carbanucleoside **90** using this methodology.



88 **89** **90**

Scheme 11. a) 2,5-amino-4,6-dichloropyrimidine, TEA, EtOH; b) 1. $CH(OEt)_3$, HCl, 2. HCl, THF-H_2O.

Later improvements in the Traube synthesis represent the use of a formylated pyrimidine species.[85] These easily obtainable reagents[86] denote a significant enhancement in yields and, thanks to their higher reactivity, the employment of milder reaction conditions. Also, substitution of triethyl ortoformate with diethoxymethyl acetate and the use of microwave irradiation signify a step forward in these transformations. Saneyoshi *et. al.*, from group of prof. Marquez, used this approach in the synthesis of **93**,[85d] a precursor for one of the methanocarbaadenosine derivatives.

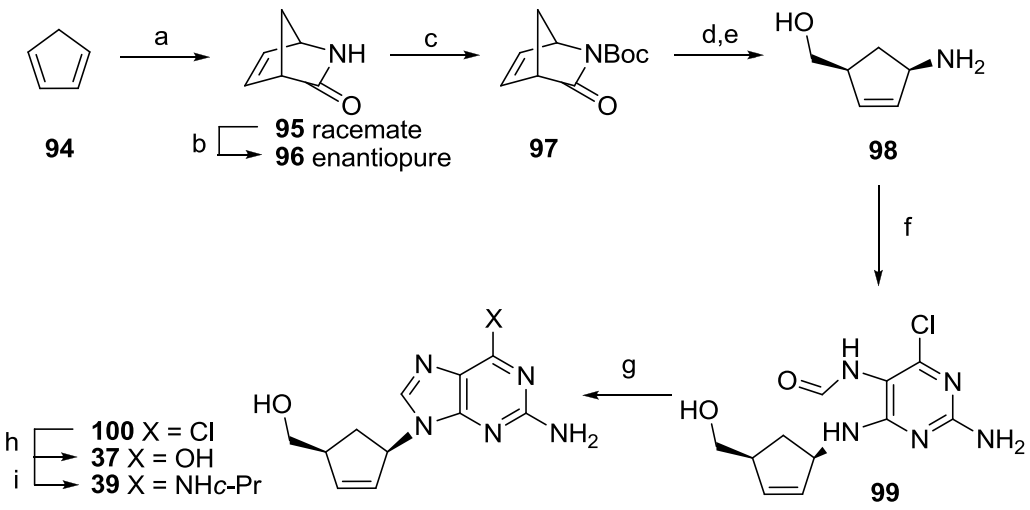


91 **92** **93**

Scheme 12. a) 2-amino-4,6-dichloro-5-formamidopyrimidine, DIPEA, dioxane, MW; b) $(EtO)_2CHOAc$, MW.

1.3.3. Carbocyclic nucleosides - Abacavir

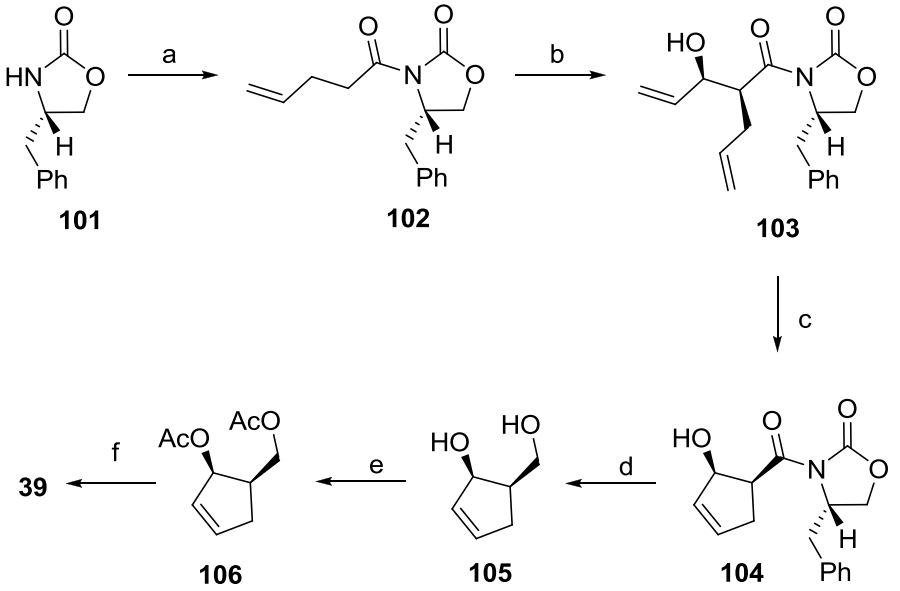
Abacavir **39** (ABC, Ziagen®) is a commercially available anti-HIV drug. It is a prodrug of its predecessor Carbovir **37**, which was eliminated from drug development due to its pharmacological deficiencies. Original synthesis of carbovir by Vince *et. al.*[87] is in principle used in later, scalable syntheses of abacavir, which is currently used on an industrial scale. This impressive optimization work performed by Daluge *et. al.*[86b] from Glaxo company starts from racemic lactam **95** (also called "Vince lactam"), product of Diels-Alder reaction between cyclopentadiene **94** and tosyl cyanide. Lactamase enzymatic resolution provided enantiomerically pure **96**, which was in three simple steps converted to the direct precursor of Abacavir, amine **98**. In the assembly of the 2-amino-6-chloropurine nucleobase authors use the above mentioned 2-amino-4,6-dichloro-5-formamidopyrimidine and also describe an elegant and efficient preparation of this reagent.



Scheme 13. a) 1. Tosyl cyanide, 2. AcOH; b) enzymatic resolution (lactamase); c) Boc_2O, DMAP, THF; d) $NaBH_4$, THF-MeOH; e) HCl, EtOH; f) 2-amino-4,6-dichloro-5-formamidopyrimidine, TEA, EtOH; g) $CH(OEt)_3$, HCl (cat.); h) NaOH, H_2O; i) cyclopropylamine, EtOH.

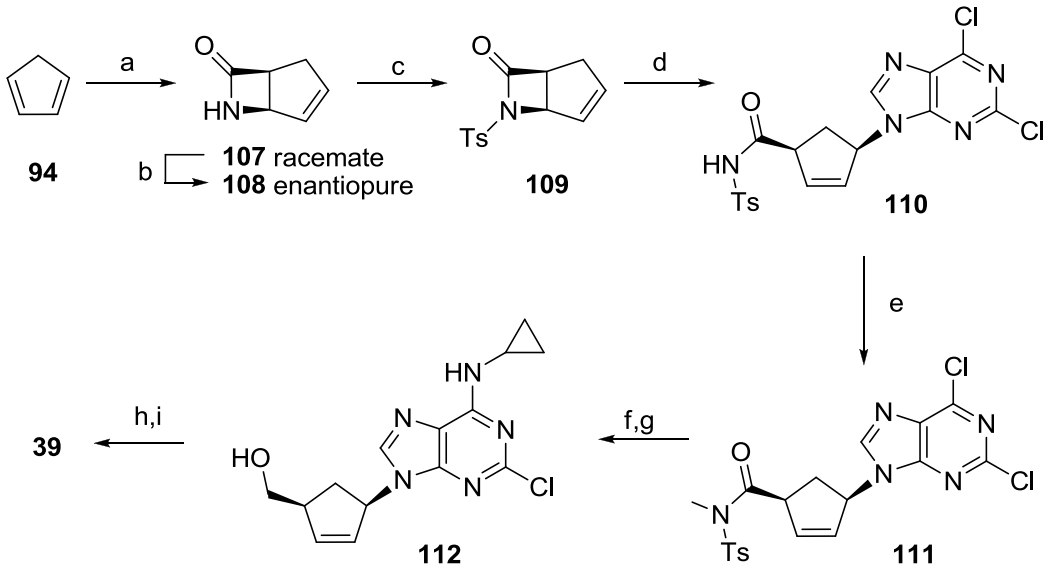
As Abacavir became successful and well known, a number of different approaches to synthesize this molecule emerged. The synthesis performed by Crimmins *et. al.*[88] starts from commercial (*S*)-4-benzyl-2-oxazolidinone **101** from which the key olefin **103** is prepared in two steps. Ring closing olefin metathesis followed by reduction of the oxazolidine moiety yields diolic cycloalkene **105**, which after acetylation is submitted to the Tsuji-Trost coupling with 2-amino-6-

cyclopropylaminopurine. The use of this nucleobase in the coupling step interestingly resulted in good N-9/N-7 selectivity (95:5). Crimmins also used this protocol to devise a solid phase synthesis of Abacavir-like carbocyclic nucleosides.



Scheme 14. a) *n*-BuLi, THF, pentenoic-pivalic mixed anhydride; b) Bu_2BOTf, TEA, acrolein, DCM; c) Grubbs cat., DCM; d) $LiBH_4$, THF-MeOH; e) Ac_2O, TEA, DMAP, DCM; f) 2-amino-6-cyclopropylaminopurine, $Pd(PPh_3)_4$, NaH, THF-DMSO.

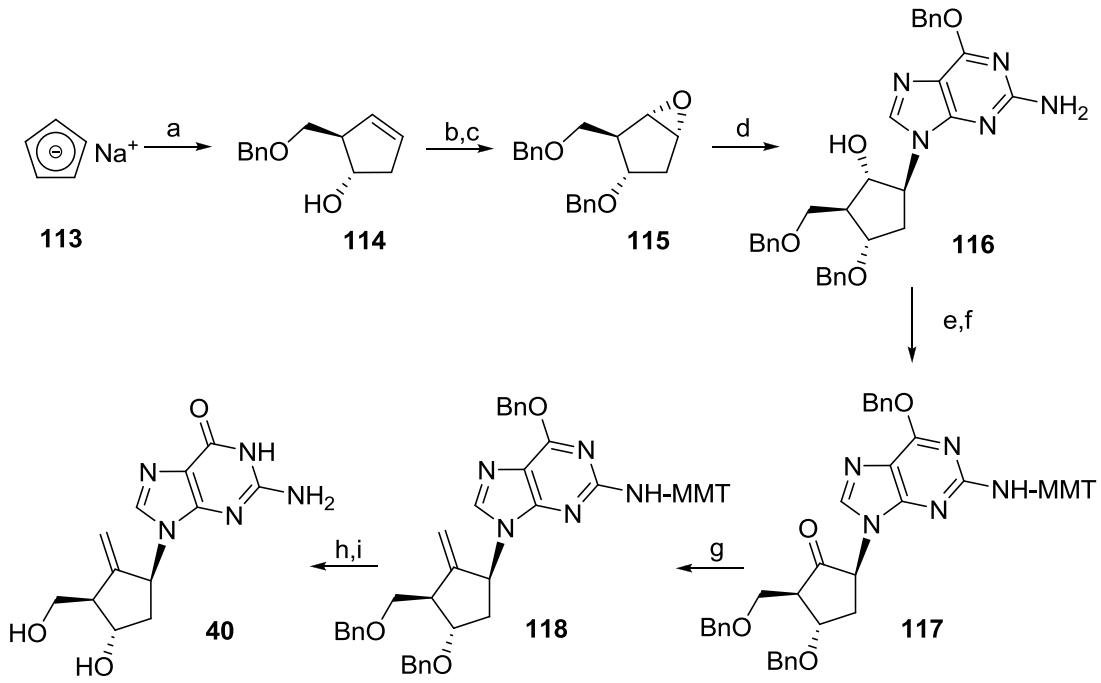
A very recent approach toward the synthesis of Abacavir has been published by Boyle *et. al.*.[89] This synthesis starts from β-lactam **107**, which is accessible in enantiomerically pure form *via* [2+2] cycloaddition of cyclopentadiene **94** and chlorosulfonyl isocyanate followed by resolution with lipase. This lactam is subsequently tosylated to furnish **109**, which is used for direct introduction of 2,6-dichloropurine by means of allylpalladium complex. Reaction of the tetrabutylammonium salt of the nucleobase catalyzed by $Pd_2(dba)_3$ afforded **110** in an impressive 75% yield. Transformations on both pseudosugar ring and the nucleobase leading to Abacavir **39** were performed in 5 further steps.



Scheme 15. a) Chlorosulfonyl isocyanate, benzene; b) eznymatic resolution (lipase); c) *p*-Ts_2O, DMAP, TEA, DCM; d) (2,6-dichloropurine)$^-$-$(Bu_4N)^+$, $Pd_2(dba)_3$, $P(Oi\text{-}Pr)_3$, THF; e) MeI, K_2CO_3, acetone; f) $NaBH_4$, THF; g) cyclopropylamine, EtOH; h) 1. NH_2NH_2, MeOH, 2. $NaNO_2$, AcOH; i) $SnCl_2$, EtOH.

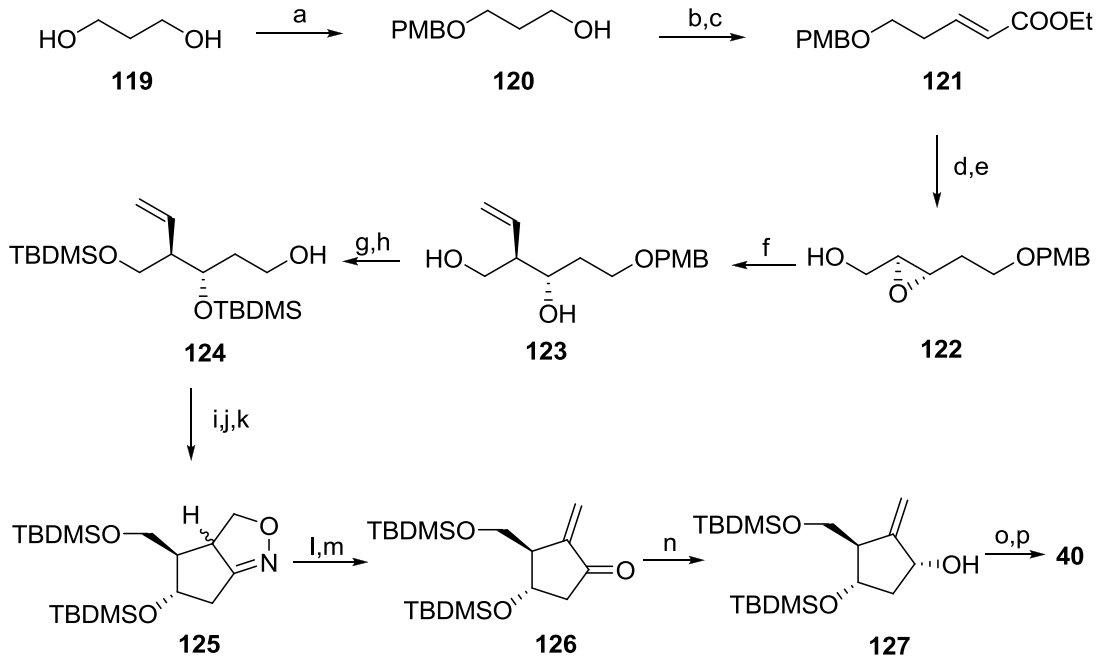
1.3.4. Carbocyclic nucleosides - Entecavir

Entecavir (ETV, Baraclude®, Entaliv®) is a 2'-deoxyguanosine analogue used in the therapy of HBV. The unusual feature of its structure is the exocyclic double bond replacing the furanose oxygen of natural 2'-deoxyribose. The original synthesis published in 1997 by Bisacchi *et. al.*[90] from the Bristol-Myers Squibb research institute starts with alkylation of the sodium salt of cyclopentadiene **113** with benzyl chlormethyl ether and subsequent hydroboration of the product, which proceeds enantioselectively. Epoxidation of the double bond of the resulting **114** affords **115** and its oxirane function is nucleophilically opened with O-benzyl guanine forming a carbocyclic nucleoside analogue **116**. After protection of the nucleobase's amino function and the Dess-Martin oxidation, the methylene group is introduced by the means of Nysted olefination of **117**. Two step deprotection then furnishes Entecavir **40** in 18% overall yield. Used starting material is crucial in this synthesis, author claims that **113** obtained from a commercial supplier or isolated from cyclopentediene and sodium hydride reaction proved superior to *in situ* prepared reagent using sodium metal.



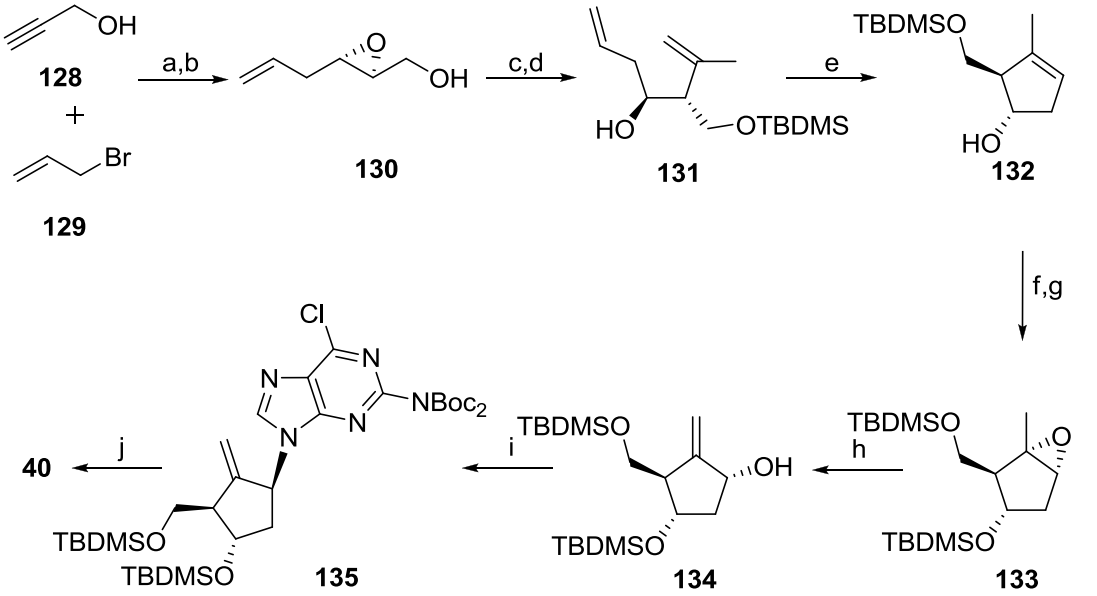
Scheme 16. a) 1. $BnOCH_2Cl$, THF, 2. diisopropylcamphenylborane, THF, 3. NaOH, H_2O_2; b) $VO(acac)_2$, *t*-BuOOH, DCM; c) BnBr, NaH, *n*-Bu_4NI, DMF; d) 2-amino-6-benzyloxypurine, LiH, DMF; e) 4'-monomethoxytrityl chloride, TEA, DMAP, DCM; f) Dess-Martin reagent, *t*-BuOH, DCM; g) Nysted reagent, $TiCl_4$, THF; h) HCl, THF-MeOH; i) BCl_3, DCM.

In other reports of Entecavir synthesis, the nucleobase was introduced by means of the Mitsunobu reaction, therefore alcohol precursors were required. Zhou *et. al.*[91] start their very recently published total synthesis from 1,3-propandiol **119** and although it might seem to be rather lenghty, its simplicity, cheap reagents and standard conditions together with 23% overall yield makes it an interesting competition to previously reported procedures. In the first three steps the chain is elongated by two carbons using Wittig reaction forming olefin **121**. After reduction of the ester functionality, the olefin double bond is submitted to enantioselective Sharpless epoxidation and the resulting optically pure **122** is opened with allylmagnesium bromide to form **123**. After the exchange of protecting groups the branched olefin **124** is converted in three steps to a mixture of isoxazolines **125**, which is hydrogenolysed on Pd/C in aqueous THF containing $B(OH)_3$. The resulting hydroxyl ketone is, without purification, treated with mesylchloride providing enone **126**, which is stereoselectively reduced with $LiBH(Et)_3$ to the key allylic alcohol **127** suitable for Mitsunobu reaction with benzylated guanine.



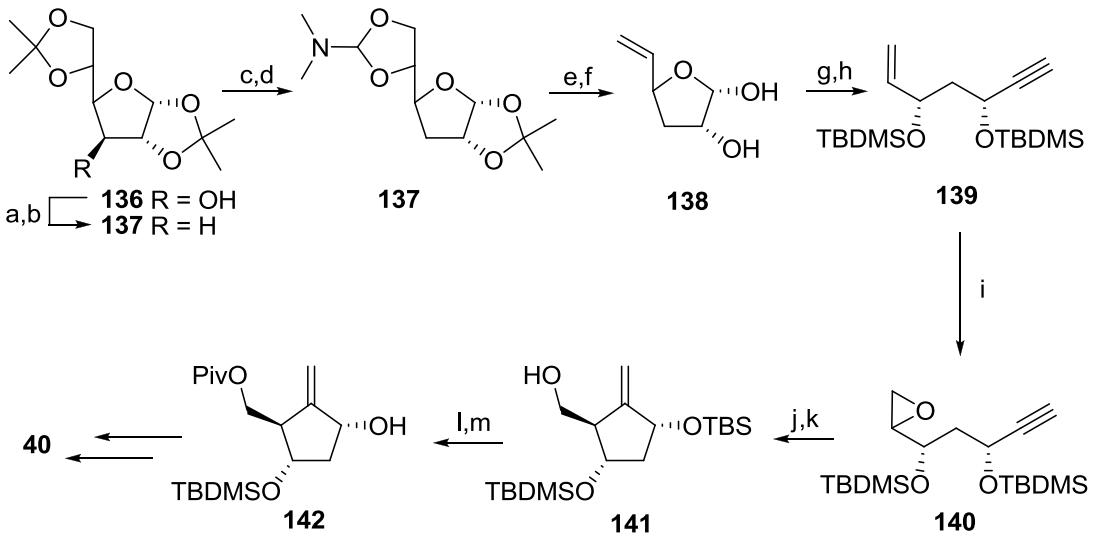
Scheme 17. a) PMBCl, NaH, TBAI, DMF; b) $(COCl)_2$, DMSO, TEA; c) PPh_3=CHCOOEt; d) DIBAL-H, THF; e) Ti(*i*-PrO)$_4$, L-(+)-DEPI, *t*-BuOOH, DCM; f) CH_2=CHMgBr, CuI, THF; g) TBDMSCl, imidazole, DMF; h) DDQ, DCM; i) $(COCl)_2$, DMSO, TEA; j) NH_2OH, AcONa, MeOH; k) NaClO, DCM; l) H_2, Pd/C, $B(OH)_3$, THF-H_2O; m) MsCl, TEA, DCM; n) $LiBH(Et)_3$, THF; o) O-benzylguanine, PPh_3, DEAD, THF; p) HCl, dioxane.

Another recently published synthesis by Liu *et. al.*[92] employs ring closing metathesis as a key reaction leading to a suitably substituted cyclopentane ring **132**. **131**, a substrate for this reaction can be obtained by a copper-catalyzed reaction of epoxide **130** with Grignard reagent. Selective vanadium acetoacetate mediated epoxidation of **132** with *tert*-butyl peroxide led to **133** and crucial alcohol **134** was obtained via epoxide isomerization. Protected 2-amino-6-chloropurine nucleobase was again introduced by the means of Mitsunobu reaction and acid-catalyzed deprotection connected with hydrolysis of the nucleobase to guanine furnished entecavir in high overall yield.



Scheme 18. a) In, THF; b) *t*-BuOOH, D-diethyl tartrate, Ti(O*i*-Pr)$_4$, DCM; c) isopropenyl magnesium bromide, CuI, THF; d) TBDMSCl, imidazole, DMF; e) Grubbs cat. DCM; f) *t*-BuOOH, VO(acac)$_2$, ClCH$_2$CH$_2$Cl; g) TBDMSCl, imidazole, DMF; h) diethylaluminium 2,2,6,6-tetramethyl piperidine, toluene; i) 2-NBoc$_2$-6-chloropurine, DEAD, PPh$_3$, THF; j) HCl, THF.

Many syntheses of carbocyclic nucleosides start from a suitably protected sugar. Ziegler *et. al.*[93a] reported a synthesis of entecavir starting from diacetone-D-glucose, which includes several very interesting reactions. First the C-3 hydroxy group was removed by Bu$_3$SnH forming 3-deoxy sugar **137**. Then the olefin **138** was formed using amide acetal procedure and isopropylidene deprotection. Using Ohira protocol[93b], **138** was converted to acetylenic diol **139**, which was, after protection of the hydroxyl groups with TBDMS, converted to epoxide **140** with *m*CPBA. Crucial for the whole reaction sequence is the cyclization of this epoxide to methylene cyclopentane **141**, which the authors optimized to 82% yield with no *cis*-isomer present in the reaction mixture. Another synthetic challenge is the selective desilylation of pivaloylated **141** to **142** which authors managed to afford only in modest yield. Entecavir can also be prepared from **142** using Mitsunobu reaction.



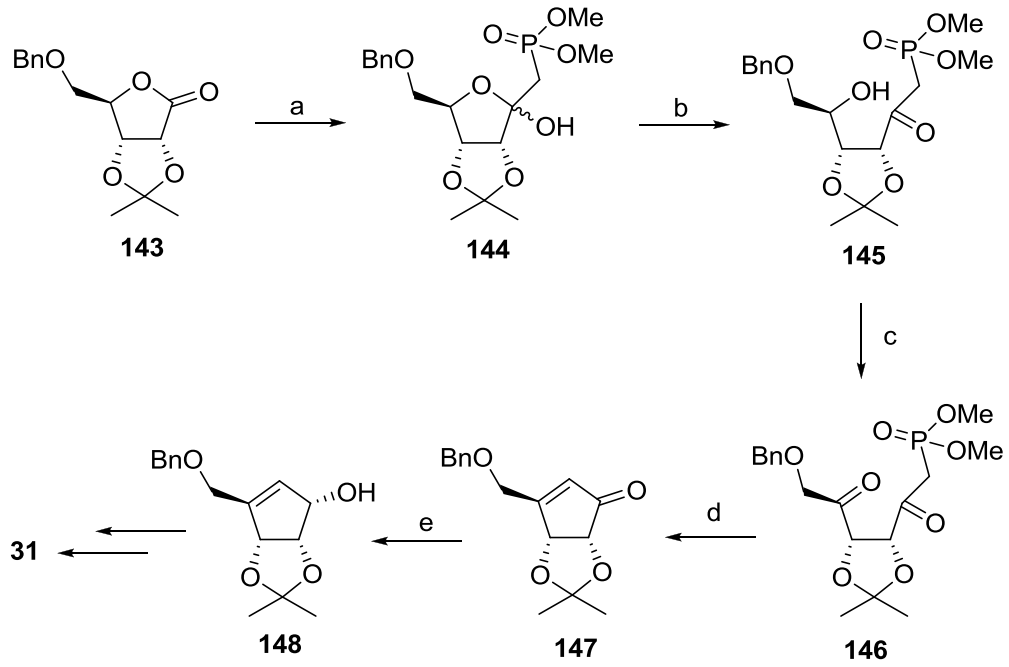
Scheme 19. a) NaH, THF, CS_2, MeI; b) $(Bu_3Sn)_2O$, AIBN, PMHS, *n*-BuOH, toluene; c) 30 % AcOH; d) $(MeO)_2CHNMe_2$, toluene; e) Ac_2O; f) 4% H_2SO_4, THF; g) $(MeO)_2POCN_2COMe$, K_2CO_3, MeOH; h) TBDMSOTf, 2,6-lutidine, DCM; i) *m*CPBA, DCM; j) Cp_2TiCl, THF; k) 4% H_2SO_4; l) PivCl, DMAP, pyridine; m) 80 % AcOH.

1.3.5. Conformationally locked carbocyclic nucleosides - Methanocarbathymidines

Methanocarbathymidines, extensively studied by the group of prof. Marquez,[69,94] represent a great contribution to the study of the relationship of carbocyclic nucleosides' conformation with their antiviral activity. Two basic structures of these direct thymidine analogues locked in North (N-MCT **48**) and South (S-MCT **49**) conformation are depicted in Figure 16. Although these two bicyclo[3.1.0]hexane-based compounds would be predicted to have the same mechanism of action due to the sole difference being their conformations, they exerted significantly different antiviral activities against HSV-1 and HSV-2. N-MCT is a better inhibitor than acyclovir, while S-MCT is devoid of any activity.[69,94c] Studies using tritium-labeled structures show, that although the South conformer is more efficiently phosphorylated in cells (higher levels of phosphorylated S-MCT than N-MCT), its negligible amounts incorporated into DNA implies that the North conformer is significantly preferred by DNA polymerase.[94c]

It is also noteworthy that N-MCT is active against Kaposi sarcoma, caused by Human herpesvirus 8 (HHV-8)[94d] and its adenine analogue is effective against EBV and HCMV.[94e]

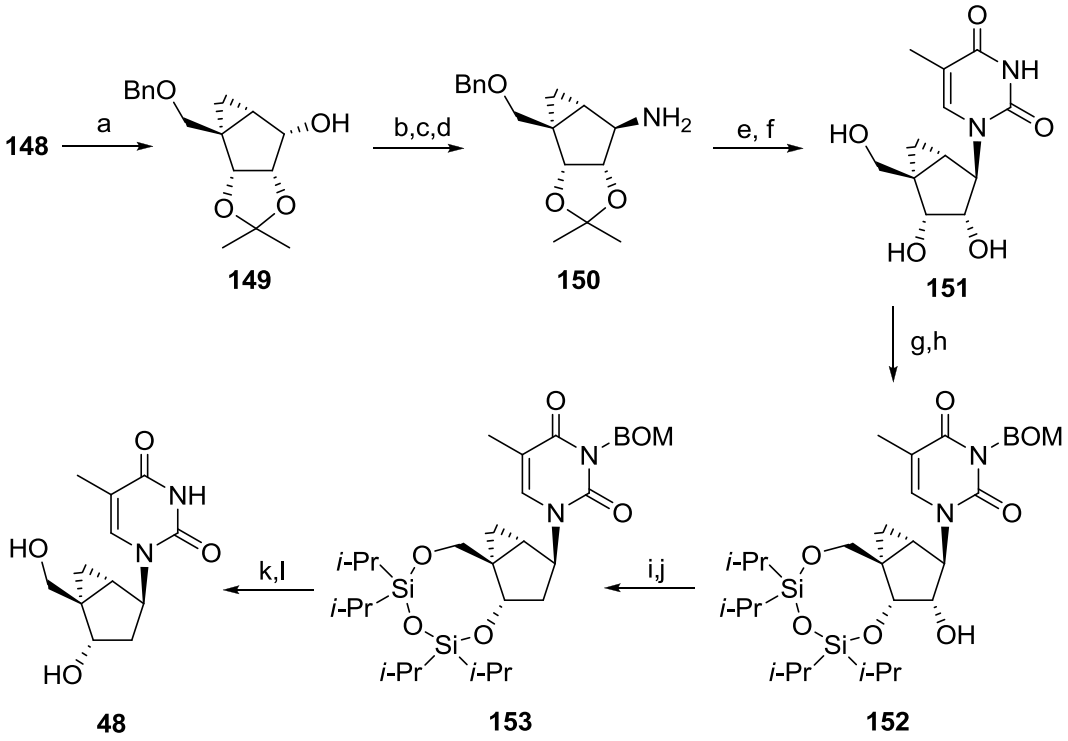
The first synthesis of N-MCT was published by Altmann *et. al.*[95] and was based on previous work performed by Marquez on the synthesis of Neplanocine A.[96] Preparation of the crucial synthon **148** started from a protected ribonolactone **143**, which was treated with dimethyl methylphosphonate lithium salt to furnish **144**. This hemiketal was subsequently opened with sodium methoxide and this open form tautomer of **145** was then oxidized using Collins reagent. Resulting diketone **146** underwent intramolecular cyclization to **147**, cyclopentenone, from which a single enantiomer was obtained by crystallization. The keto group was reduced with sodium borohydride to afford **148**.



Scheme 20. a) $LiCH_2P(O)(OMe)_2$, THF; b) MeONa, MeOH; c) CrO_3, pyridine; d) K_2CO_3, 18-crown-6, benzene; e) $NaBH_4$, $CeCl_3$, MeOH.

Altmann's synthesis starts with Simmons-Smith cyclopropanation of **148**, which affords **149** stereoselectively due to the directing effect of the allylic hydroxy group. **149** is then converted to **150** containing amino group with inverted configuration relatively to **149** hydroxyl by a sequence of tosylation, nucleophilic displacement of the tosylate with sodium azide and hydrogenation of the azide. The thymine

nucleobase was then constructed on this amine and both isopropylidene and benzyl protecting groups were removed to afford **151**. The 2'-OH group had to be removed in order to obtain 2'-deoxythymidine analogue. N-3 position of thymine was protected with BOM and 3' and 5' hydroxy groups were protected using TIPDSi prior to conversion of 2'-OH to corresponding thiocarbonate, which was cleaved radically with tributyl tinhydride. Resulting compound **153** was purified on chiral HPLC column and deprotection of both pseudosugar and nucleobase yielded final N-MCT **48**.

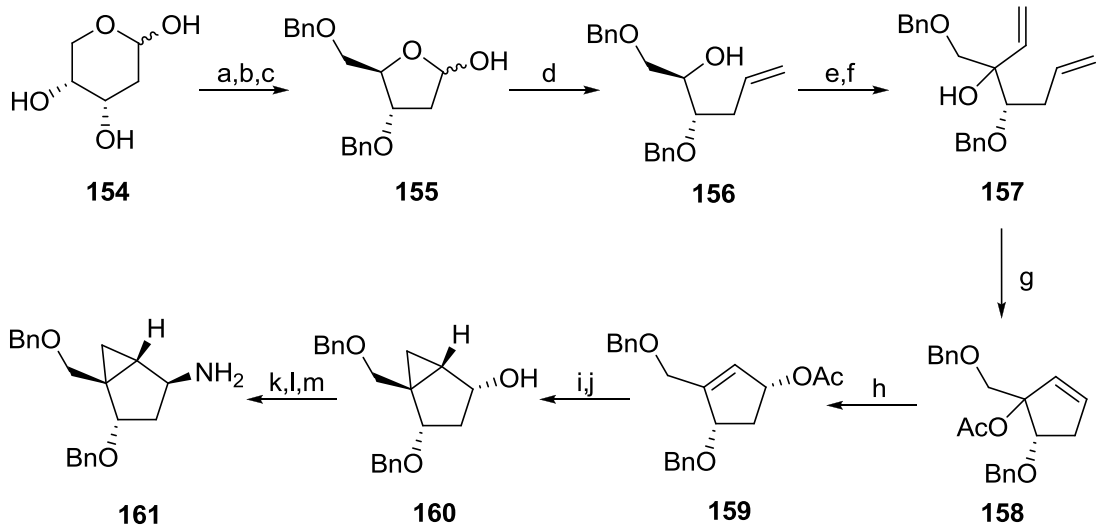


Scheme 21. a) Zn/Cu, CH_2I_2, Et_2O; b) TsCl, TEA, DCM; c) NaN_3, DMF; d) H_2, Lindlar cat.; e) 1. $CH_3OCH{=}C(CH_3)CONCO$, DCM, 2. HCl, EtOH-H_2O; f) H_2, Pd/C, AcOEt-MeOH; g) $TIPDSiCl_2$, imidazole, DMF; h) BOMCl, DBU, MeCN; i) $CH_3PhOC(S)Cl$, DMAP, TEA, DCM; j) Bu_3SnH, AIBN, DME; k) TBAF, THF; l) H_2, Pd/C, MeOH.

It is apparent that this reaction route is very long and tedious, therefore better and simpler routes to these compounds had to be discovered.

An interesting strategy has been devised by Ludek and Marquez, where authors start their synthesis from 2-deoxy-D-ribose **154**.[94f] In 6 steps a diene **157** suitable for ring-closing metathesis is prepared. Wittig transformation of **155** afforded **156**, which was subjected to Swern oxidation and then reaction with vinylmagnesium

bromide affording **157** in acceptable yield. Protected cyclopentene triol **158** was rearranged to **159** using bis-(acetonitrile)palladium dichloride and, similarily to original synthesis, Simmons-Smith reaction was used to introduce the annelated cyclopropane ring into the molecule. Alcohol **160** was converted to amine **161** in the same manner as in the previous synthesis and the thymine nucleobase was constructed on its amino group.



Scheme 22. a) CH_3COCl, MeOH; b) NaH, BnBr, *n*-Bu_4NI, THF; c) CH_3COCl, H_2O-dioxane; d) Ph_3PCH_2Br, *n*-BuLi, THF; e) $(COCl)_2$, DMSO, TEA, DCM; f) vinylmagnesium bromide, THF; g) Grubbs' cat., DCM; h) *p*-benzoquinone, $PdCl_2(MeCN)_2$, THF; i) NaOH, MeOH; j) Et_2Zn, CH_2I_2, DCM; k) MsCl, TEA, DCM; l) NaN_3, DMF; m) H_2, Lindlar cat.

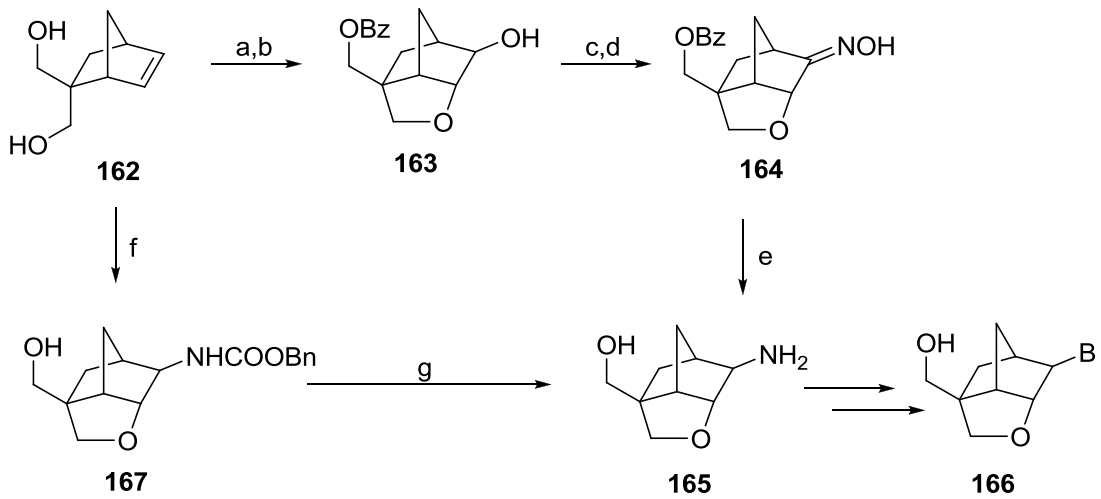
1.3.6. Norbornane-based conformationally locked carbocyclic nucleosides

A very extensive contribution to the field of conformationally locked carbanucleosides comes from the work of Hřebabecký and coworkers.[84c,97] In the last decade a wide library of conformationally locked carbocyclic nucleosides based on norbornane, bicyclo[2.2.2]octane and bicyclo[3.2.1]octane have been synthesized with many interesting antiviral hits. These compounds were originally aimed against HIV, however they have been later found remarkably active against Coxsackievirus B3 (CVB-3).

In principle, the approaches to these compounds can be divided to two types according to the introduction of the nucleobase. In the vast majority of cases it was introduced by means of either Mitsunobu reaction of an alcohol precursor or

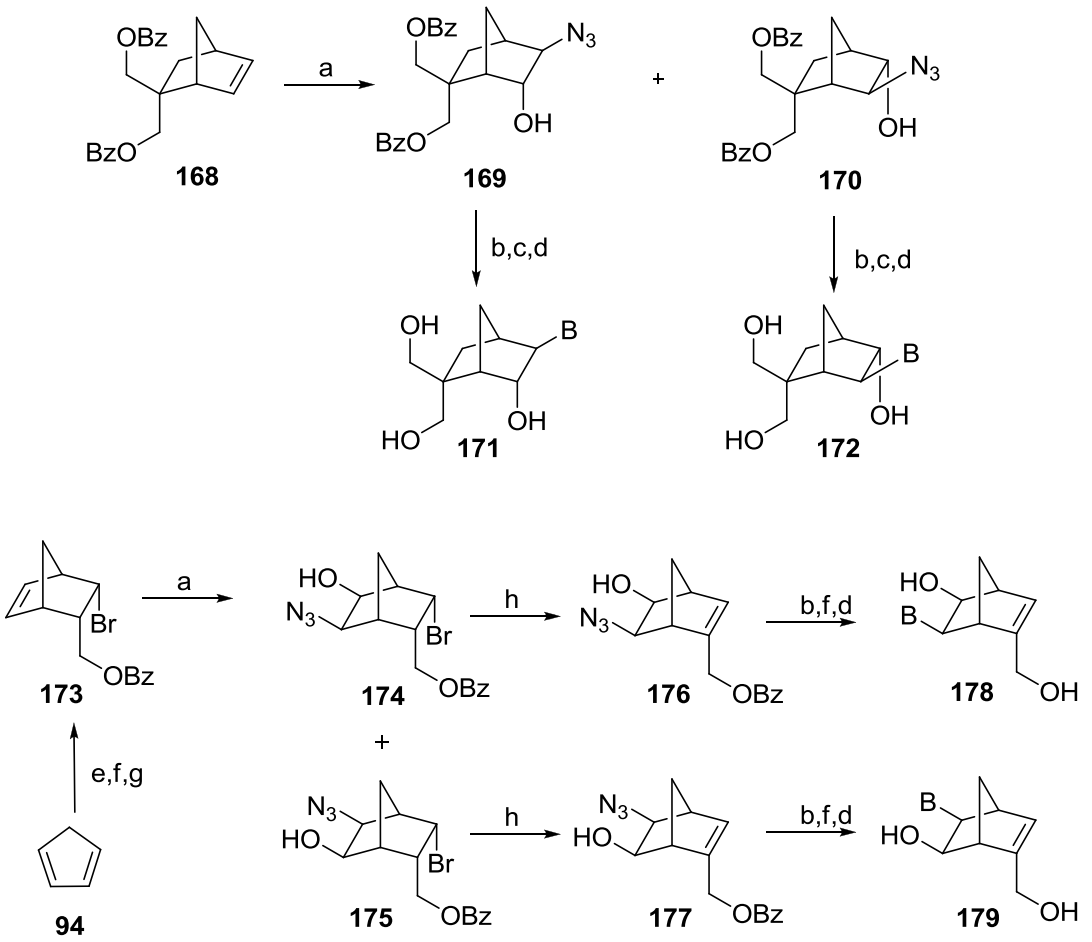
heterocycle construction on a corresponding amine. Very important in these syntheses is also easy access to starting norbornane precursors. Some are commercially available, but the majority were synthesized by means of Diels-Alder reaction between cyclopentadiene or polychlorinated cyclopentadiene as a diene and a suitable dienophile.

Tricyclic derivatives consisting of the general formula **166** were synthesized in the earliest work.[97a] Upon epoxidation of the starting bicyclic precursor **162** the etheric ring was closed by the intramolecular ring-opening reaction. A necessary amino group was introduced by the reduction of a corresponding oxime **164**, prepared by PDC oxidation of **163** and subsequent reaction of the resulting ketone with hydroxylamine hydrochloride. In an alternative route the amino function is introduced by adding benzyl azidoformate to the double bond of compound **162** and by intramolecular nucleophilic opening of the resulting triazine ring with *endo*-hydroxymethyl yielding tricyclic protected amine **167**.



Scheme 23. a) *m*CPBA, $CHCl_3$; b) BzCl, pyridine; c) PDC, DCM; d) NH_2OH-HCl, AcONa, MeOH; e) $LiAlH_4$, THF; f) benzyl azidoformate, toluene; g) H_2, $Pd(OH)_2$/C, MeOH.

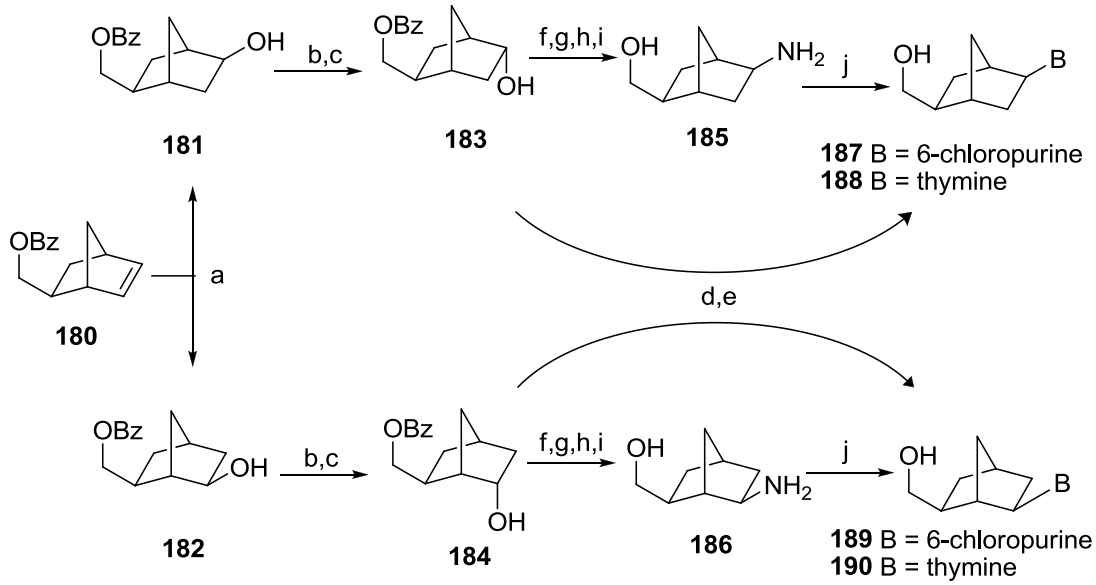
Another interesting pathway to functionalized norbornyl amines is represented by the addition of chromyl azide to a double bond. In this fashion compounds **171**, **172**, **178** and **179** with a hydroxy group vicinal to a nucleobase can be obtained.[97b,c] The only drawbacks of this synthesis are very laborous separations of the resulting regioisomers and the fact that chromylazide is explosive.



Scheme 24. a) CrO_3, NaN_3, AcOH; b) MeONa, MeOH; c) H_2, $Pd(OH)_2/C$, MeOH; d) Nucleobase construction; e) ethyl (2*Z*)-3-bromoacrylate, BBr_3, DCM; f) $LiAlH_4$, THF; g) BzCl, pyridine; h) DBU, HMPA.

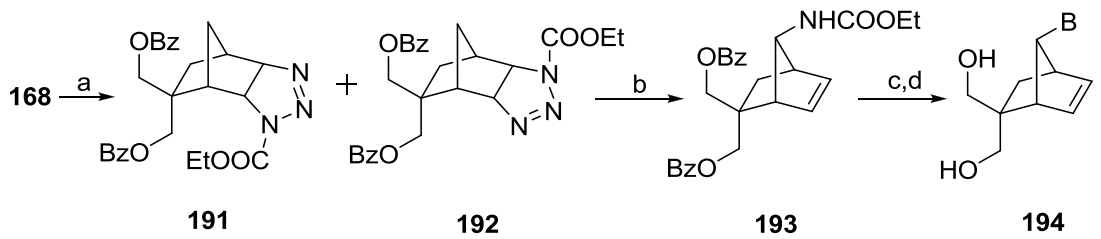
Although the use of Mitsunobu reaction as the convergent approach to nucleobase introduction is simple and straightforward and the precursors for its employment are often more simply accessible, in many cases lower reactivity of certain nucleobases and/or amine substrates requires use of the build-up approach. The necessary amino group can be introduced for instance by nucleophilically displacing the tosylate or mesylate of the original alcohol with an azide followed by the azide's subsequent reduction.

An example of such situation is depicted in the Scheme 25, where Mitsunobu reaction of **183** or **184** with 6-chloropurine yielded **187** and **189**, respectively, without difficulties, but experiments with N-3 benzoyl thymine failed. For the synthesis of thymine derivatives **188** and **190** it was necessary to prepare amines **185** and **186**, respectively and construct the nucleobase afterwards.[97e]



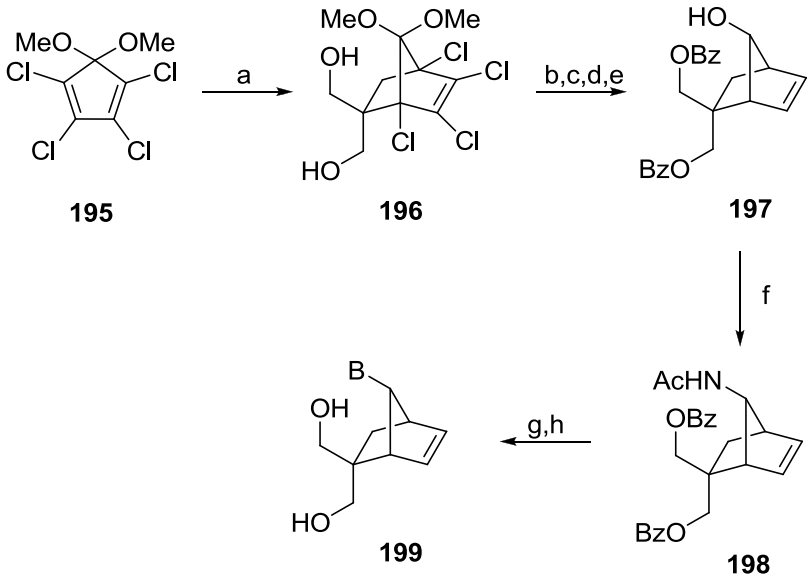
Scheme 25. a) 1. BH_3, THF, 2. $NaBO_3$, H_2O; b) PDC, DCM; c) $NaBH_4$, MeOH; d) 6-chloropurine, PPh_3, DIAD, THF, e) DIBAL-H, DCM; f) MsCl, pyridine; g) NaN_3, DMF; h) MeONa, MeOH; i) H_2, $Pd(OH)_2/C$, MeOH; j) thymine construction.

Another possible method of amino group introduction was used in the synthesis of norbornane-based compounds bearing the nucleobase in the C-7 position - the shorter bridge of the bicyclic skeleton.[97f] In the first depicted synthesis, reaction of functionalized norbornene **168** with ethylazidoformate followed by silica gel-mediated decomposition of triazoline structure accompanied with Wagner-Meerwein rearrangement led to protected amine **193**, which was then deprotected and, using nucleobase construction protocol, converted to final compound **194**.



Scheme 26. a) Ethylazidoformate, toluene; b) silica gel, DCM; c) KOH, EtOH-H_2O; d) nucleobase construction.

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **195** represents a good starting material to compounds similar to **194**.[97f] Preparation of a protected amine **198** with opposite configuration to **193** in the C-7 position starts with Diels-Alder reaction of **195** with acrolein followed by formation of diol **196** by the reaction with formaldehyde. Chlorine atoms are then removed by the reaction with sodium in liquid ammonia, hydroxymethyl groups protected with benzoyl and ketal in the C-7 position converted to an alcohol, giving rise to compound **197**. This alcohol was transformed to an amine with the same configuration by means of Ritter reaction with sulfuric acid using acetonitrile as a source of nitrogen. Structure **199** was obtained after nucleobase construction.

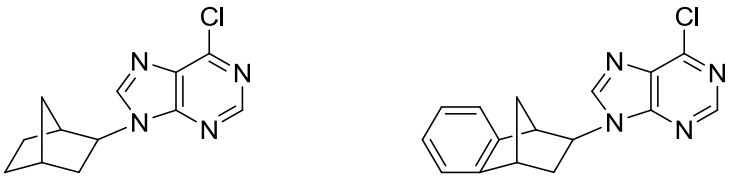


195 **196** **197** **198** **199**

Scheme 27. a) 1. Acrolein, 2. aq. HCHO; b) Na, NH_3, THF-EtOH; c) BzCl, pyridine; d) Dowex 50 (H^+), dioxane-H_2O; e) $NaBH_4$, THF-H_2O; f) MeCN, H_2SO_4-AcOH; g) KOH, EtOH-H_2O; h) nucleobase construction.

Very important for further work on norbornane based compounds was the discovery of compound **200** by Šála *et. al.*[97g,h] Although its structure and synthesis are rather simple, its anti-Coxsackievirus activity is remarkable and ignited further search for even better CVB-3 inhibitors. Using this compound, it was proven that the hydroxymethyl group, which would be essential for phosphorylation in cells, is not necessary for this particular antiviral activity. Although many of these structures should be considered more as N-alkylated nucleobases than nucleoside analogues,

their structural features and origin should justify their inclusion into this group of compounds.



200

CVB-3: EC_{50} = 0.81±0.20 μM
CC_{50} > 50 μM

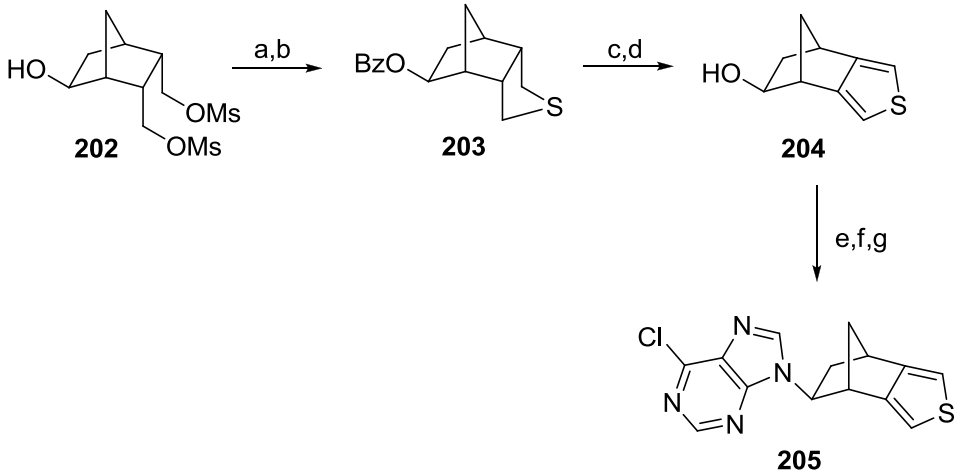
201

CVB-3: EC_{50} = 0.66±0.35 μM
CC_{50} > 50 μM

Figure 18. Most active anti-Coxsackie compounds reported by Šála.[97g,h]

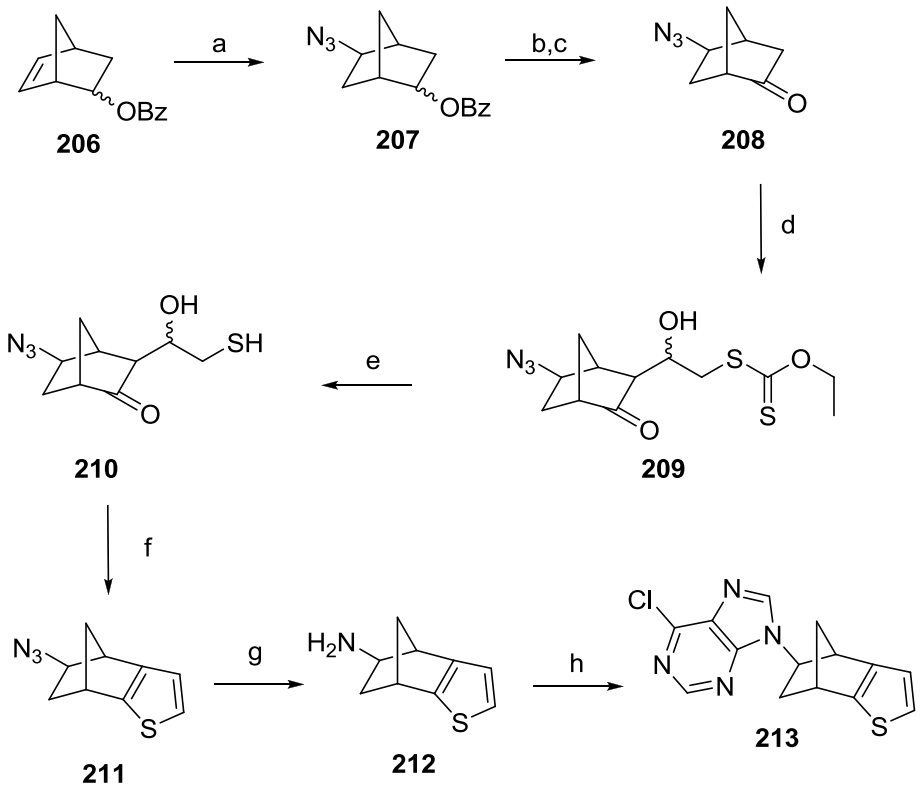
The search for more active anti-CVB-3 compounds was rewarded with the discovery of a more potent compound **201**[97g] with a benzene ring annelated in the 5,6 position of the norbornane skeleton. Bearing in mind that thiophene is a bioisostere of benzene, compounds with an annelated thiophene, as well as other aromatic rings, have been synthesized recently.[97i] Their synthesis is, however, more complicated since these aromates are poor substrates for the Diels-Alder reaction.

The synthesis of a 3,4-annelated thiophene analogue is straightforward - ring closure of the dimesylate **202** with Na_2S afforded compound **203** with annelated tetrahydrothiophene ring, which was then aromatized to **204**. Configuration of a hydroxy group on the opposite side of the molecule was inverted to provide alcohol substrate suitable for Mitsunobu reaction with 6-chloropurine yielding **205**.



Scheme 28. a) $Na_2S \cdot 9H_2O$, DMF; b) BzCl, pyridine; c) DDQ, chlorobenzene; d) MeONa, MeOH; e) DMSO, $(CF_3CO)_2O$, TEA, DCM; f) $NaBH_4$, MeOH; g) 6-chloropurine, PPh_3, DIAD, THF.

2,3-Annelated derivatives represent a bigger synthetic challenge. At first the azido group was introduced into the skeleton **206** *via* azidomercuration reaction. The ketone-containing intermediate **208** was then prepared by deprotection and Swern oxidation of **207** and vicinally to this ketone a carbondithiolate sidechain was installed using aldol reaction. Acid catalyzed cyclization of **210** and aromatization formed azide **211** and reduction of the azido group furnished amine **212** suitable for nucleobase construction.



Scheme 29. a) 1. NaN_3, $Hg(OAc)_2$, THF, 2. KOH, $NaBH_4$; b) MeONa, MeOH; c) DMSO, $(CF_3CO)_2O$, TEA, DCM; d) 1. $(TMS)_2NLi$, THF, 2. $ZnCl_2$, OCH-CH_2-S-C(S)-OCH_2CH_3; e) 1-methylpiperazine; f) HCl, THF; g) $LiAlH_4$, THF; h) 1. 5-amino-4,6-dichloropyrimidine, TEA, EtOH, 2. $CH(OEt)_3$, HCl.

2. Aims of the Thesis

- Development of new strategies for the preparation of variously substituted norbornane skeletons with special respect to the Diels-Alder reactions of cyclopentadiene and the introduction of substituents to the bridgehead position(s).

- Development of a novel strategy for purine nucleobase construction in order to simplify and speed up this transformation as well as increase its yields.

- Synthesis of conformationally locked carbocyclic nucleosides with nucleobase, hydroxymethyl or both in the bridgehead position of the norbornane skeleton. Evaluation of the influence of the pseudosugar pucker on the antiviral activity of these compounds.

- Synthesis of N-alkylated nucleobases based on the bridgehead substituted norbornane to expand the library of potential anti-CVB-3 compounds.

3. Results and Discussion

3.1. Novel protocol for the Diels-Alder reaction leading to variously substituted norbornene precursors used in further syntheses

Over the last decade our team has synthesized a large library of norbornane-based carbocyclic nucleosides and the most common starting materials for these compounds - variously substituted norbornanes - are best obtained using the Diels-Alder [4+2] cycloaddition reaction. These compounds also represent an important structural motif in organic chemistry in general. Norbornanes have been discovered to be a part of various natural products,[98] are present in commonly used catalysts,[99] industrial intermediates and additives,[100] pharmaceutical and cosmetic products,[101] and are also invaluable precursors in organic synthesis[102].

Polyhalogenated norbornanes have been used on an industrial scale for decades (e.g. pesticides, flame retardants, plasticizers).[103] However these chlorine-rich compounds were later discovered to be poorly biodegradable and were labeled "persistant organic pollutants" (POPs) by the Stockholm Convention.[104] Together with notoriously know DDT or polychlorinated biphenyls, compounds such as Aldrine **214**, Chlordane **215**, Mirex **216** and others, which were until 1970s used in enormous quantities all over the world, are now banned for commercial use in the western world. Nevertheless polychlorinated hydrocarbons are still valuable starting materials in organic synthesis, such as in the preparation of natural products.[105]

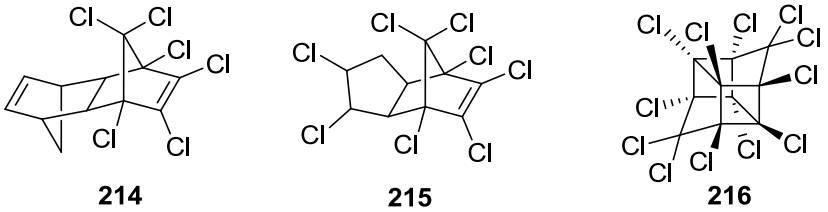


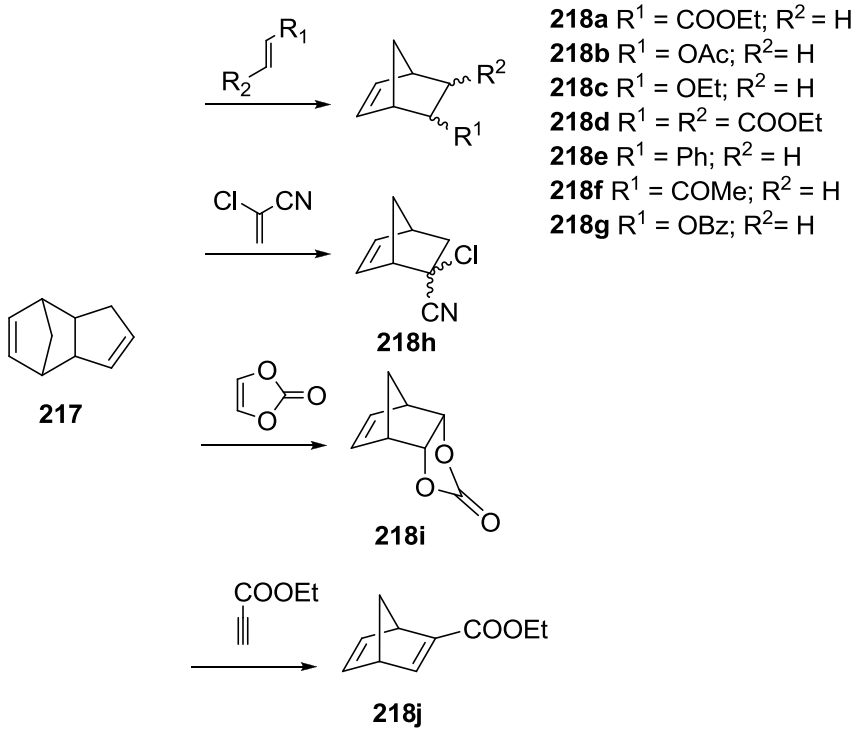
Figure 19. Pesticides based on polychlorinated norbornanes.

Although the Diels Alder reaction is very well mapped using a wide variety of conditions, reagents and solvents[106] (e.g. use of Lewis acids or copper[106b] to catalyze the reaction or use of ionic liquids as solvents[106c]), I have decided to explore further possible inovations with a special respect to speed, efficiency and simplicity, which would allow the preparation of larger quantities of products without the use of expensive additives.

3.1.1. Reactions employing dicyclopentadiene

The most common preparation of 5,6-disubstituted norbornenes involves the simple reaction of cyclopentadiene with a suitable dienophile. This reaction, however popular, has one serious disadvantage - it includes laborious cracking of dicyclopentadiene, which is not only ineffective,[107] but on larger scale might be dangerous[108], and industrial accidents including fatal injuries have been recorded.[109] Huertas *et. al.*[110] recently circumvented this drawback by trapping *in situ* generated cyclopentadiene with a dienophile. Even so, his approach is limited solely to high boiling dienophiles (reaction temperature up to 200° C) which designates the scope of this work to be rather narrow. Several literature records employing microwave irradiation in Diels-Alder reaction exist,[111] but never have these two methods been merged into one procedure, which would combine the simplicity of trapping the *in situ* generated cyclopentadiene, and the reduced reaction time of using the microwave irradiation, therefore allowing the use of low boiling dienophiles.

I have observed that heating a mixture of dicyclopentadiene and an appropriate dienophile in a microwave reactor slowly leads to the formation of the cycloadduct even at 130°C. Reasonable reaction speed is achieved at 150°C with most reactions reaching completion in 1 hour and only those with bulkier dienophiles requiring longer reaction times. Due to rather poor microwave absorption of reagents, temperatures over 150°C could not be easily achieved and reactions with vinyl acetate and ethyl vinyl ether were not executable at all because temperatures higher than 120°C could not be reached. Vinyl acetate was, however, succesfully replaced with vinyl benzoate whose microwave absorption proved to be better. Sufficient conversion was determined with GC-MS analysis and the isolation of products was accomplished either by column chromatography (hexane - ethyl acetate mobile phase) or, on a larger scale, *via* distillation.



Scheme 30. Hydroquinone (cat.), 150°C, MW, 1-5 h (Table 1).

Table 1. Diels-Alder reactions of dicyclopentadiene and appropriate dienophile[a]

Ent.	Product	Time (min)	Temp. (°C)	Conv. (%)[b]	*Endo/Exo*[c]	Yield[d](%)
1	**218a**[112a]	90	150	97	2/1	80
2	**218b**	-	-	n.r.	-	-
3	**218c**	-	-	n.r.	-	-
4	**218d**[112b]	60	150	91	-	82 [89]
5	**218e**[112c]	300	150	93	4/1	80
6	**218f**[112d]	90	150	93	1/1	80 [79]
7	**218g**[112e]	300	150	96	7/2	82 [78]
8	**218h**[112f]	60	150	96	1/3	76
9	**218i**[112g]	60	150	97	21/1	84
10	**218j**[112h]	60	150	88	-	35

[a] Reaction conditions: dicyclopentadiene **217** (1 mmol), dienophile (2 mmol), hydroquinone (10 mg), microwave irradiation. [b] Determined by GC-MS. [c] Determined by ^{1}H-NMR. [d] Isolated yields. Yields of multigram experiments isolated by distillation are in square brackets.

I was particulary interested in the reaction with ethyl propiolate, which afforded only a poor yield (35%). I have therefore attempted it under similar conditions with conventional heating in a steel autoclave, however a dark-brown solid of polymeric agglomerate containing only traces of product was obtained.

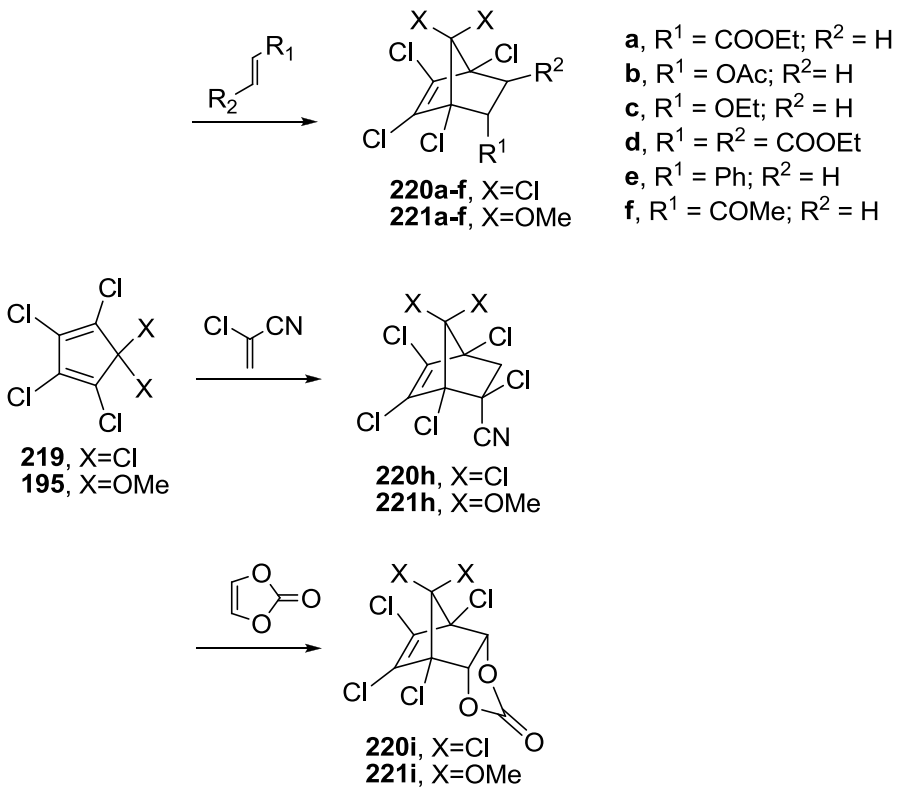
An important feature of the Diels-Alder reaction is the stereoisomeric ratio of *endo/exo* products. According to Alder's rule the *endo* product is kinetic and the *exo* product is thermodynamic and on the reaction with maleic anhydride or 1,4-benzoquinone, it has been shown that the more quickly formed *endo* product can be thermically converted to the more stable *exo* derivative.[106a] As expected, my reactions afforded mixtures of stereoisomers (with the exception of **d** and **j**) with *endo* usually being predominant. The ratio of products was determined using NMR spectroscopy followed by comparison with literature data.

3.1.2. Reactions employing polychlorinated cyclopentadienes

The use of polychlorinated cyclopentadienes may be beneficial when diastereoselectivity of the reaction is a key factor, because these reactions provide only one stereoisomer due to steric repulsion of C-7 substituents. The use of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **195** also allows the simple introduction of an oxygen substituent to norbornane C-7 position, which is otherwise not an easily feasible transformation.

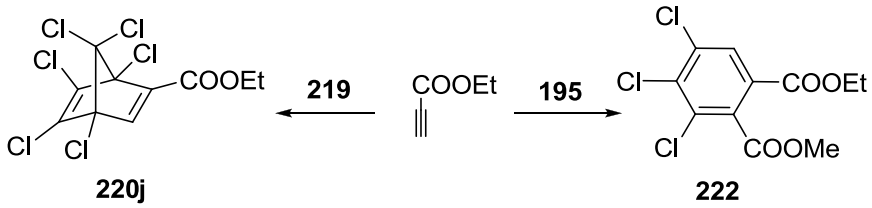
Typical conditions of these reactions previously reported in the literature consist of conventional heating (sealed vessel or reflux in open vessel) of a diene and dienophile mixture (mostly excess of dienophile) in nonpolar high-boiling solvents such as toluene or xylene.[112,113] This procedure is mostly sluggish with reaction times ranging from several hours to even days.

I have discovered that heating an equimolar mixture of chlorinated cyclopentadiene with an appropriate dienophile (containing <1% hydroquinone as antipolymeration agent) in the microwave at temperatures ranging from 130 to 180°C resulted in up to 100-fold shorter reaction times (even < 2 minutes) and afforded very good to quantitative yields. Observed diastereoselectivity was quantitatively *endo* and the combination of this method with the dechlorination procedure using sodium in liquid ammonia represents a simple approach to *endo*-5-substituted norbornenes with the possibility of protecting the keto group in the C-7 position.



Scheme 31. Hydroquinone (cat.), 130-180°C, MW, 2-60 min (Table 2).

As expected from literature precedent[114], the reaction of **195** with ethyl propiolate was connected with a thermal rearrangement and afforded the benzene derivative **222**, while reaction with **219** proceeded normally to the norbornane derivative **220j**.



Scheme 32.Hydroquinone (cat.), 150°C, MW, 30 min (Table 2).

Completion of the reactions was determined using GC-MS and products were isolated either by column chromatography (hexane - ethyl acetate) or by crystallization from methanol with a few drops of water. Only crude **220h** and **220i** had to be filtered through a plug of silica before crystallization in order to decolorize and "pre-purify" the product. Some of the compounds may also be distilled at reduced pressure as was shown on a scale-up preparation of **220a**.

Table 2. Diels-Alder reactions of polychlorinated cyclopentadiene and appropriate dienophile[a]

Ent.	X	Product	Time (min)	Temp. (°C)	Conv. (%)[b]	Yield[c](%)
1	**Cl**	**220a**[113a]	2	150	95	81 (72)
2	**Cl**	**220b**[113b]	45	180	92	81 [81]
3	**Cl**	**220c**[113c]	40	150	48	31
4	**Cl**	**220d**[113b]	60	180	62	36
5	**Cl**	**220e**[113d]	2	150	98	95 (84)
6	**Cl**	**220f**[113e]	5	150	96	84 (70)
7	**Cl**	**220h**[113f]	60	130	77	66 (52)
8	**Cl**	**220i**[113g]	10	150	96	71 (63)
9	**Cl**	**220j**[113h]	30	150	86	69
10	**OMe**	**221a**[113i]	2	150	100	80
11	**OMe**	**221b**[113j]	30	180	97	75 (66)
12	**OMe**	**221c** [113k]	30	150	98	79
13	**OMe**	**221d**	30	180	98	72
14	**OMe**	**221e**[113l]	2	150	100	93
15	**OMe**	**221f** [113l]	5	150	100	75 (69)
16	**OMe**	**221h**[113f]	10	150	100	69
17	**OMe**	**221i**[113g]	10	150	100	76 (73)
19	**OMe**	**222**	30	150	86	70

[a] Reaction conditions: polychlorinated cyclopentadiene **219** or **195** (2 mmol), dienophile (2 mmol), hydroquinone (10 mg), microwave irradiation. [b] Determined by GC-MS. [c] Yields isolated by column chromatography. In parentheses yields isolated by crystallization. In square brackets yields of multigram experiment isolated by distillation.

3.1.3. Recapitulation

A simple, fast and easy method for the synthesis of various norbornene derivatives was developed. A main feature is also the fact that no additional reagents and no solvents are necessary for the reaction and that the purification of products is possible only using distillation or crystallization, which makes this method very cheap and attractive for large-scale preparations. It is also worth mentioning that the reactions of dicyclopentadiene could be carried out at temperatures lower than the temperature commonly used for cyclopentadiene preparation, thus allowing the

Diels-Alder reaction to take place even with low-boiling dienophiles at reasonable pressure (below 5 bar).

Results of this project were published in *Synthesis* in 2011.[115]

3.2. Novel modification of the Traube synthesis leading to variously substituted purines

The introduction of a purine nucleobase represents without doubt one of the key transformations in the synthesis of nucleosides. A brief review on possible convergent and linear methods for this reaction is included in Chapter 1.3.1. and 1.3.2. Here it is necessary to mention that for the introduction of the nucleobase to a tertiary carbon only the build-up approach is usable, which specifically applies to the bridgehead positions of bicyclic and polycyclic skeletons.

Besides nucleosides, there is also a myriad of other purine-containing molecules which have interesting biological activities and are worth studying. Variously substituted purines have been found to possess antimicrobial[116] or anticancer[117] properties, inhibit various cell kinases[118] or to be active against human parasites[119]. The appearance of substituted purines in biologicaly active molecules both naturally occurring[120] and synthetic[121] has been recently nicely reviewed.

To avoid the difficulties and drawbacks commonly associated with the Traube synthesis modifications, I have decided to explore the fact that the use of triethyl orthoformate or diethoxymethyl acetate in the imidazole ring closure step practically means the introduction of a masked formyl group to the molecule. If the formylated reagents mentioned in chapter 1.3.2. (4,6-Dichloro-5-formamidopyrimidine **223** and 2-Amino-4,6-dichloro-5-formamidopyrimidine **224**) are used under different reaction conditions, the imidazole ring closure might take place directly in the same pot without the need of any additional reagents.

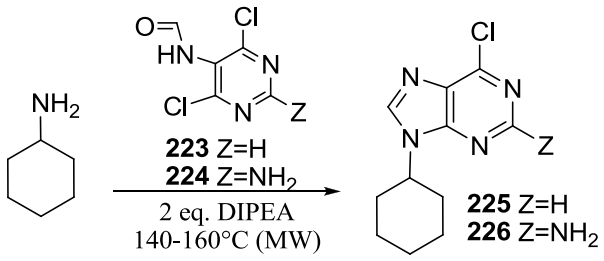
3.2.1. Determination of the optimum reaction conditions

I have observed that a mere increase in reaction temperature and the use of a sealed reactor vessel (microwave or conventionally heated) does indeed close the imidazole ring directly and leads to the production of 6-chloropurine or 2-amino-6-chloropurine derivatives in a short one pot reaction. A series of optimization

experiments was performed in order to determine the best conditions for this reaction where a number of different solvents and non-nucleophilic bases were employed at various temperatures. Cyclohexylamine was selected as a model substrate for its availability and moderate reactivity (amino group on a secondary carbon).

Completion of reactions was determined using HPLC-MS analyses. Yields were determined using quantitative HPLC analysis referenced on pure sample of each product and these results, as a comparison to isolated yields, are listed in tables 3-5 in parentheses. All HPLC-MS and HPLC analyses were performed by ing. Eva Zborníková.

Table 3. Solvent selection study of one-pot purine build-up reaction



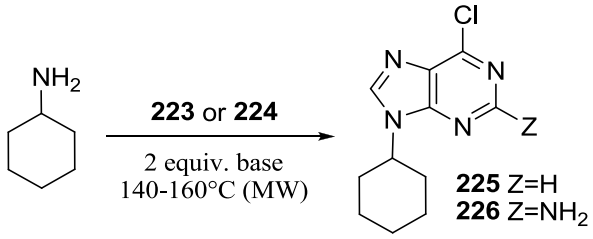
	225 (Z = H)					**226** (Z = NH_2)			
Ent.	Solvent	T	Temp [°C]	Yield [%][a]	Ent.	Solvent	T	Temp [°C]	Yield [%][a]
1	Toluene	2 h	140	80 (83)	9	Toluene	2 h	160	58 (68)
2	Dioxane	2 h	160	86 (90)	10	Dioxane	2 h	160	(66)
3	DMF	1 h	160	72[b]	11	DMF	1 h	160	69[b]
4	MeCN	2 h	140	(50)	12	MeCN	2 h	160	(62)
5	*n*-BuOH	2 h	140	73 (78)	13	*n*-BuOH	2 h	160	64 (69)
6	*i*-PrOH	2 h	140	61 (62)	14	*i*-PrOH	2 h	155	(56)
7	EtOH	2 h	140	58 (60)	15	EtOH	2 h	145	(54)
8	EtOH/H_2O[c]	2 h	140	(25)	16	EtOH/H_2O[c]	1 h	140	64 (71)

[a] Isolated yields. The yields in parentheses are HPLC-determined (HPLC analyses performed by Eva Zborníková). [b] Isolated yield of 6-dimethylamino derivative. [c] Mixture 1:1 (*v/v*).

Surprising results arose from the evaluation of solvents, where no clear dependence of the results on the solvent polarity could be recognized. All types of solvent can be employed for this reaction aside from the 6-chloropurine assembly ,

which afforded low yields in EtOH - water mixture (1:1, *v/v*). Dipolar aprotic solvents are useable, however if the reaction is carried out in DMF, C-6 chlorine atom is substituted with a dimethylamino group. This fact is in full agreement with findings published by Čechová *et. al.*[122]. For the non-nucleophilic base evaluation the three best solvents for each reaction were selected and a series of organic and inorganic bases was examined. Despite the DIPEA, also known as Hünig's base, being the best non-nucleophilic base in this study, the use of TEA afforded comparable results.

Table 4. Non-nucleopbilic base selection study of one-pot purine build-up reaction



225 (Z=H)		Toluene		Dioxane		*n*-BuOH	
Ent.	Base	Cond.[b]	Yield[c] [%]	Cond.[b]	Yield[c] [%]	Cond.[b]	Yield[c] [%]
1	DIPEA	A	80 (83)	B	86 (90)	C	73 (78)
2	TEA	A	80 (84)	B	83 (86)	C	71 (74)
3	K_3PO_4	B	(41)	C	0[d]	D	0[d]
4	K_2CO_3	B	(50)	C	0[d]	D	0[d]
5	2,6-Lutidine	C	76 (81)	B	(50)	A	61 (64)
6	Proton Sponge	A	(30)[f]	B	(38)[f]	A	(40)[f]

226 (Z=NH_2)		Toluene		*n*-BuOH		EtOH/H_2O[a]	
Ent.	Base	Cond.[b]	Yield[c] [%]	Cond.[b]	Yield[c] [%]	Cond.[b]	Yield[c] [%]
7	DIPEA	B	58 (68)	B	64 (69)	C	64 (71)
8	Et_3N	B	(65)	B	(68)	C	(67)
9	K_3PO_4	D	0[d]	D	0[d]	D	0[d]
10	K_2CO_3	D	0[d]	D	0[d]	D	0[d]
11	2,6-Lutidine	A	54 (62)	D	(35)[e]	D	(54)[e]
12	Proton Sponge	D	(30)[f]	A	(37)[f]	A	58 (66)

[a] Mixture 1:1 (*v/v*). [b] Sealed microwave reactor. Conditions A) 140°C / 2h; B) 160°C / 2h; C) 140°C / 1h; D) 120°C / 1 h. [c] Isolated yields. In parentheses are HPLC-determined yields (HPLC analyses performed by Eva Zborníková). [d] Complicated reaction mixture. [e] Reaction time had to be prolonged to 4 hours in order to reach the full conversion.Yields are diminished due to occurrance of 6-alkoxy derivatives (more significant at temperatures >120°C). [f] Nucleophilic adduct at the position C-6 with the base.

3.2.2. Reactions with various amine substrates

To prove the versatility and robustness of this method, I have employed 15 additional amines in both of these purine constructions. DIPEA was used as the non-nucleophilic base and the two best solvents were used for each of the reactions - dioxane and *n*-butanol for 6-chloropurine and *n*-butanol and EtOH-water mixture (1:1 *v/v*) for 2-amino-6-chloropurine. The use of toluene was also considered, however low solubility of products in toluene made manipulation of the reaction mixtures unpleasant and some reproducibility issues emerged as well.

Reactions were first performed in a microwave reactor and then in a sealed Ace® tube with a back seal bushing heated in an aluminium block. The conventionally heated experiments were carried out by Soňa Kovačková, PhD.

Typical conditions for the procedure consists of heating a mixture of an amine (1 mmol), a pyrimidine precursor **223** or **224** (1.2 mmol) and DIPEA (2 mmol for a free amine substrate and 3 mmol for a hydrochloride salt) in a selected solvent (5 mL) for a specified period of time. Very insoluble products **238** and **253** could be filtered off from the reaction mixture directly, which afforded products of sufficient purity upon washing with a water-methanol mixture, methanol and ethyl acetale. Other compounds were purified chromatographically on silica (**225**-**237**, **242**-**252**) or on C-18 silica (reverse phase, **239**-**241**, **254**-**256**). Products were further crystallized if possible.

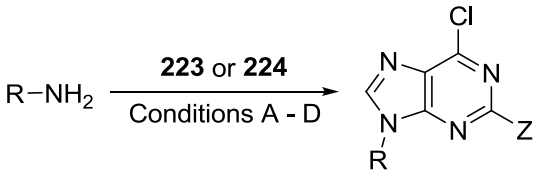
Results of these reactions are listed in table 5 and they indicate, that both polar and non-polar substrates undergo this reaction with yields ranging from good to near quantitative.

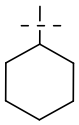
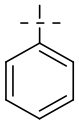
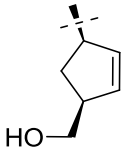
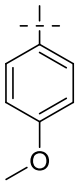
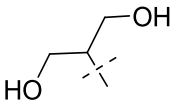
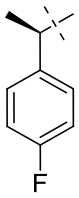
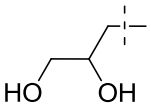
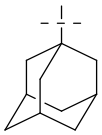
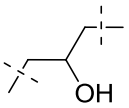
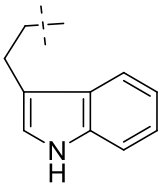
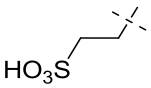
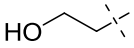
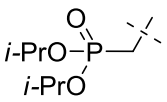
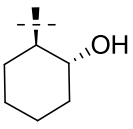
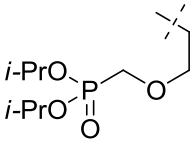
Build-up of 2-amino-6-chloropurine on an aromatic amine (**227**, **228**, **242**, **243**) in *n*-butanol afforded nice yields of the product without any difficulties, with an exception being in EtOH-water mixture (1:1, *v/v*), where no product was present in the reaction mixture.

Compounds containing two purine nucleobases may be prepared from substrates containing two amino groups (**238** and **253**).

Reaction with substrates containing phosphonate diester afforded phosphonate monoesters in both cases (**240, 241**, **255, 256**).

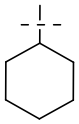
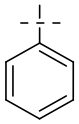
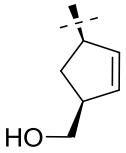
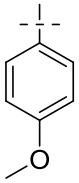
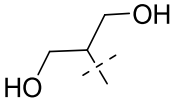
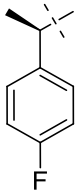
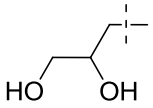
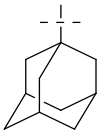
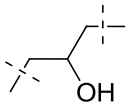
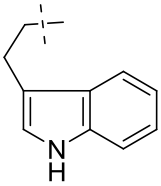
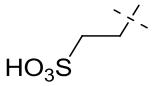
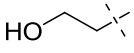
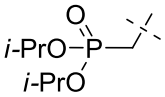
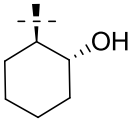
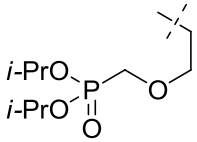
Table 5. Construction of purines on various amine substrates



		Z = H				Z = H	
Prod.	R	Cond[a]	Yield [%][b]	Prod.	R	Cond[a]	Yield [%][b]
225[123a]		A B	86 (86) 78 (74)	**234**		A B	61 [65] 51 (52)
227[123b]		A B	75 (80) 77 [85]	**235**[123d]		A B	66 (66) 70 (68)
228		A B	90 (77) 84 [87]	**236**		A B	90 (82) 88 [86]
229		A B	93 (94) 86 [94]	**237**[123e]		A B	61 [63] 66 [65]
230[123c]		A B	55 (47) 56 (35)	**238**[c]		A B	88 (83) 85 (80)
231		A B	88 (61) 93 [96]	**239**		A B	87 (83) 70 (68)
232		A B	92 (79) 84 (94)	**240**		A B	ND[d] 63 (80)[e]
233		A B	79 [82] 79 (85)	**241**		A B	ND[d] 50 (57)[e]

[a] A: dioxane, 160°C / 2h; B: *n*-BuOH, 140°C / 2h. [b] Isolated yields of MW heated experiments. Isolated yields of conventionally heated experiments are in parentheses. Yields of conventionally heated experiments determined with HPLC are in brackets (measured by Eva Zborníková). [c] A bipurine derivative is formed using 2.4 mmol of pyrimidine reagent. [d] The yield was less than 10% (HPLC based), product was not isolated. [e] Isolated yield of phosphonate monoester.

Table 5. Construction of purines on various amine substrates - continued

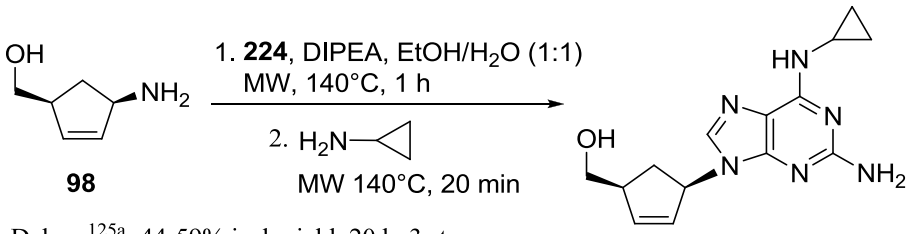
Prod.	R	Z=NH_2 Cond [a]	Z=NH_2 Yield [%][b]	Prod.	R	Z=NH_2 Cond [a]	Z=NH_2 Yield [%][b]
226[123a]		C D	69 (76) 71 (70)	**249**		C D	66 (55) 62 (60)
242[123f]		C D	62 (73) 0 (0)[c]	**250**[86b]		C D	78 (76) 80 (75)
243		C D	73 (80) 0 (0)[c]	**251**		C D	82 (74) 77 [79]
244		C D	93 (92) 55 (49)	**252**[123h]		C D	70 (82) 45 [52]
245		C D	52 (66) 57 (30)	**253**[d]		C D	86 (80) 72 (58)
246		C D	96 (97) 86 (87)	**254**		C D	71 (72) 58 [70]
247		C D	87 (82) 90 (87)	**255**		C D	ND[e] 62 (73)[f]
248[123g]		C D	82 (75) 75 (70)	**256**		C D	ND[e] 42 (43)[f]

[a] C: *n*-BuOH, 160°C / 2h; D: EtOH-H_2O (1:1, *v/v*), 140°C / 1h. [b] Isolated yields of MW heated experiments. Isolated yields of conventionally heated experiments are shown in parentheses. Yields of conventionally heated experiments determined with HPLC are in brackets (measured by Eva Zborníková). [c] Under these conditions a 6-phenylamino or 6-p-methoxyphenylamino derivative is formed. [d] A bipurine derivative is formed using 2.4 mmol of pyrimidine reagent. [e] The yield was less than 10% (HPLC based), the product was not isolated. [f] Isolated yield of phosphonate monoester.

3.2.3. Subsequent one-pot nucleophilic reactions of C-6 chlorine atom

The modification of the C-6 position is one of the most common derivatizations of the purine nucleobase, and we have therefore decided to explore the compatibility of described methodology with a one-pot performed nucleophilic displacement of the C-6 chlorine atom by simple addition of an appropriate nucleophilic reagent. Tryptamine was selected as a model substrate for this transformation and 6 different nucleophiles were employed as reagents - ammonia, primary and secondary amines, thiourea, sodium methoxide and sodium hydroxide. Results are listed in Table 6 and yields range from very good to excellent. It is also noteworthy that the reaction with thiourea could not be performed under microwave irratiadion, and those reaction yields were greatly diminished. This fact is in agreement with experince of Niu and coworkers.[124]

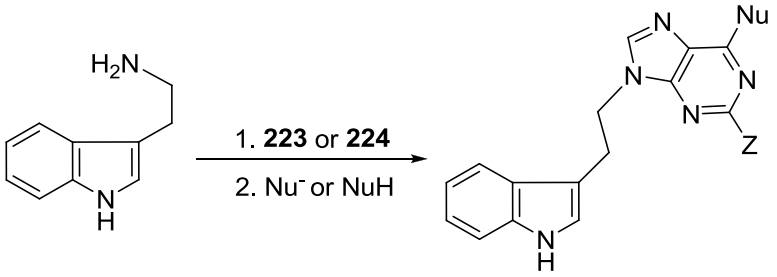
This three-step, one-pot methodology was applied to the synthesis of a commercially available drug abacavir, a carbocyclic nucleoside used in the treatment of HIV. Amine substrate **98** was obtained in three simple steps from commercially available (1*R*)-(−)-2-azabicyclo[2.2.1]hept-5-en-3-one according to literature procedure.[86b] The nucleobase construction and subsequent C-6 modification proceeded smoothly with very good overall yield and only one necessary purification procedure. Comparison with literature procedures proved this method to be superior in terms of reaction speed, laboriousness and yield.[125]

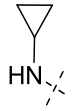
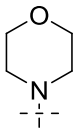
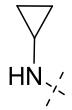
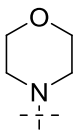


Daluge[125a]: 44-59% isol. yield, 20 h, 3 steps
Rossi[125b] : 42% isol. yield, 32 h, 4 steps
Reported : 75% isol. yield, 80 min, 2 steps, one-pot

Scheme 33. Comparison of the preparation of abacavir with literature procedures.

Table 6. Subsequent one-pot reactions of tryptamine derivatives (**231** and **246**) with various nucleophiles under microwave irradiation



Prod.	Reagent	Nu	Z	Conditions	Yield [%][a]
257	Ammonia[b]	NH_2	H	140°C/20 min, 10 eq, *n*-BuOH	86
258	Cyclopropyl-amine		H	140°C/20 min 5 eq, *n*-BuOH	91
259	Morpholine		H	140°C/20 min 5 eq, *n*-BuOH	87
260	Thiourea[c]	SH	H	100°C/4h 2 eq, *n*-BuOH	80
261	MeONa[d]	OMe	H	80°C/10 min 5 eq, Dioxane[e]	82
262	NaOH[f]	OH	H	100°C/10 min 10 eq, Dioxane[e]	79
263	Ammonia[b]	NH_2	NH_2	140°C/30 min 10 eq, *n*-BuOH	92
264	Cyclopropyl-amine		NH_2	140°C/10 min 5 eq, *n*-BuOH	82
265	Morpholine		NH_2	140°C/10 min 5 eq, *n*-BuOH	83
266	Thiourea[c]	SH	NH_2	100°C/4h 2 eq, *n*-BuOH	84
267	MeONa[d]	OMe	NH_2	100°C/10 min 5 eq, Dioxane[e]	93
268	NaOH[f]	OH	NH_2	100°C/10 min 10 eq, Dioxane[e]	88

[a] Isolated yields. [b] 3.5 M solution in ethanol. [c] The reaction could not be performed under MW irradiation[124], the reaction mixture was heated in an oil bath. [d] 1M solution in methanol. [e] 6-alkoxy derivatives are formed if the reaction is performed in alcohols. [f] 2M solution in water.

3.2.4. Recapitulation

A very convenient and simple route to variously substituted purine derivatives starting from amine substrates was developed. This is the first technique leading to 9-substituted purine derivatives in a single pot reaction, which makes it a method of choice for such transformations. Pyrimidine precursors used for this reaction are commercially available or can be easily prepared according to literature procedures.[86] Also no acidic conditions are necessary for the imidazole ring closure and therefore this reaction can be advantageously connected with the subsequent substitution of a C-6 chlorine atom using various nucleophiles.

Usefulness of this mehod was proven on the synthesis of a commercially successful anti-HIV drug, Abacavir, which was synthesized on a much shorter timescale and with a significantly higher yield compared to literature procedures.

Results of this work have been recently published[126] and a Czech patent application (PV2012-54) covering this methodology has been filed.

3.3. Synthesis of carbocyclic nucleoside analogues locked in North conformation

In this chapter the synthesis and antiviral evaluation of carbocyclic nucleosides' analogues locked in North conformation will be discussed. These compounds are based on norbornane skeleton with the nucleobase in the C-3 position of the bicycle and hydroxymethyl group in the C-1 (bridgehead) position. The discussion in this chapter will include the preparation of the substrates suitable for nucleobase introduction as well the nucleobase introduction itself, further derivatization of the purine C-6 position and phosphoramidate prodrugs synthesis.

3.3.1. Preparation of substrates suitable for the nucleobase introduction

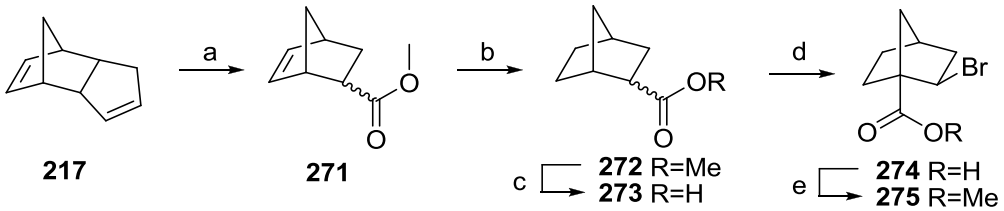
The main issue in the synthesis of norbornanes substituted in the connection of the two rings is most certainly the introduction of almost any functional group to this „bridgehead" position and then modifying this functionality to our needs. This position is not easily accessible, because a functional group there represents a sterically hindered species on a quarternary carbon and therefore cannot be targeted by nucleophilic substitutions. Moreover, the norbornane skeleton may undergo rearrangements under both acidic and basic conditions, which might lead to undesired compounds that are sometimes difficult to distinguish from the desired product.

For the North conformation derivatives I have selected two possible intermediates in regard to the nucleobase introduction. First possibility is to use the Mitsunobu reaction for which an alcohol **269** is a direct precursor and the carboxymethyl function represents a masked hydroxymethyl group. Second possibility is the nucleobase build-up on an amine precursor of the formula **270**, where no protection of the C-1 hydroxymethyl is necessary.

269 **270**

Figure 20. Desirable substrates for the nucleobase introduction.

An optimal approach for the preparation of a bridgehead substituted norbornane, published Hell-Vollhard-Zelinski bromination of **273** connected with skeleton rearrangement was selected.[127] Although the acid **273** is commercially available, a large quantity of this simple starting material was required, which led me to optimize of its preparation on a multimolar scale. Dicyclopentadiene **217** was reacted with methyl acrylate in a steel autoclave and, without purification, crude **271** was hydrogenated over palladium hydroxide and then saponified to **272**, which was purified by distillation. Overall yield of these 3 steps, including only one purification, is very nice 82%.

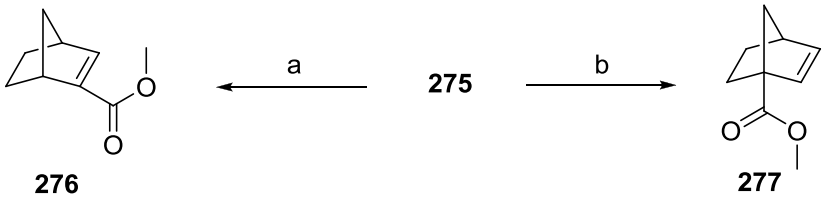


217 **271**

Scheme 34. a) Methyl acrylate, hydroquinone (cat.), 180°C, 4 h; b) $Pd(OH)_2/C$, H_2 (100 atm), MeOH, 6 h; c) NaOH, H_2O, overnight, 82% over three steps; d) Br_2, PCl_3 (cat.), 90°C, 7 h, 67%; e) MeOH, H_2SO_4 (cat.), reflux, 12 h, 84%.

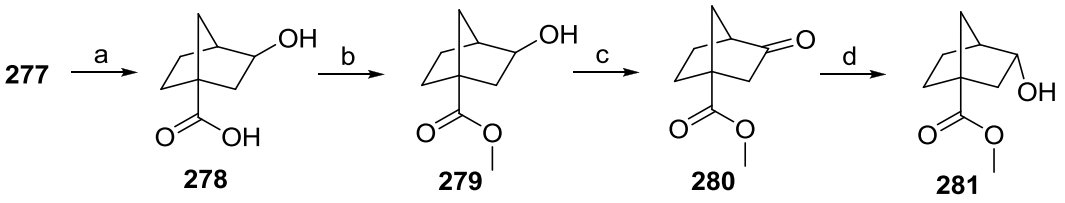
For the preparation of the crucial intermediate **278** a modified procedure published by Yates and Kaldas[128] was used. However, authors' method of elimination of the bromine atom of methyl ester **275** using *t*-BuOK proved to be highly inconvenient for larger scale reactions. Solid *t*-BuOK was impossible to use because **275** undergoes a basic-catalyzed rearrangement upon reaction with KOH,[128] which is present in the commercial reagent. Commercial solution of *t*-BuOK in *t*-BuOH is expensive, very viscous and hydrolyzes quickly when exposed to air. Also the quality of the supplied reagent was inconsistent, which led to low reproducibility of the results. After several experiments with different elimination reactions, I have

discovered that the bromine atom of **275** can be conveniently eliminated using DBU in HMPA or DMF. This reaction can be carried out without inert atmosphere and is suitable for large quantities, with an added bonus being that the product can be easily purified by extraction with hexane after dilution of the reaction mixture with water.



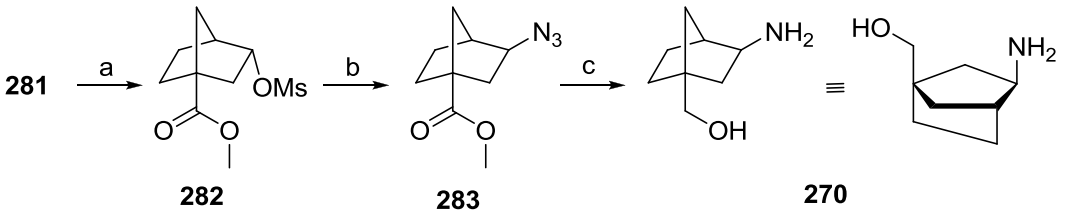
Scheme 35. a) *t*-BuOK/*t*-BuOH traces of KOH; b) DBU, HMPA, 105°C, 72 h, 72%.

Introduction of a hydroxy group into the C-3 position was accomplished by an oxymercuration reaction. Yates and Kaldas speculate in their work that electrostatic preference of one of the mercuration intermediates leads to high regioselectivity of the reaction, and indeed, **278** (ester function is hydrolyzed during workup of the reaction) was obtained as a sole product.[128] In order to obtain a suitable substrate for the Mitsunobu reaction **280**, configuration of the C-3 hydroxy group had to be inverted by means of a standard oxidation-reduction procedure.



Scheme 36. a) 1. $Hg(OAc)_2$, THF-H_2O, 2 h. 2. 3M NaOH, 30 min, 3. $NaBH_4$, 3M NaOH, 10 min, 67%; b) CH_2N_2, 10 min, 99%; c) PDC, DCM, overnight, 82%; d) $NaBH_4$, MeOH, overnight, 88%.

Amine substrate **270** was prepared in three simple steps from alcohol **281**. The *endo* hydroxyl group was mesylated and nucleophillicaly exchanged for an azido group, which was hydrogenated on palladium hydroxide.



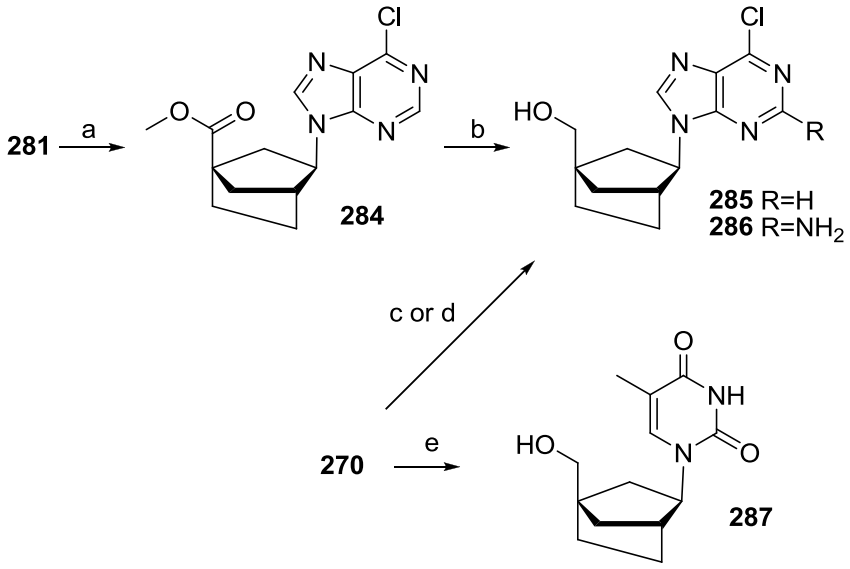
Scheme 37. a) MsCl, pyridine, 3 h, 99%; b) NaN_3, DMF, 115°C, overnight, 92%; c) $LiAlH_4$, THF, 2 h, 59%.

Although this whole linear approach seems to be rather lengthy, it must be mentioned that none of the above listed intermediates had to be purified chromatographically. Extractions, distillations and crystallizations were used for purification, which makes this route simple, cheap and usable for large scale preparation (300 g of **275** in a single batch).

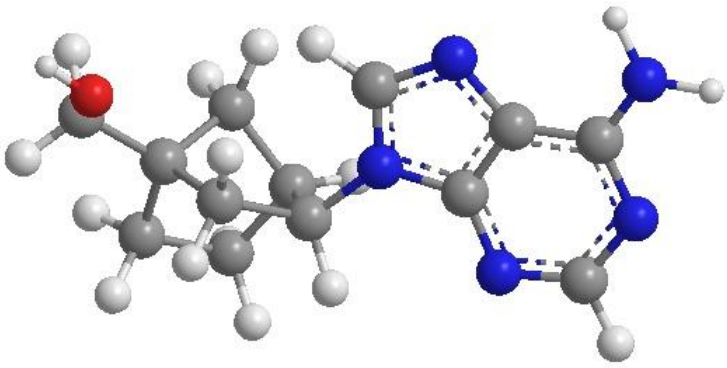
3.3.2. Nucleobase introduction, modifications of the purine nucleobase and preparation of phosphoramidate prodrugs

Both Mitsunobu reaction of **281** with 6-chloropurine and nucleobase construction on amine **270** proved useful for the preparation of carbanucleosides **285, 286** and **287**. Mitsunobu reaction of **281** afforded compound **284** in good yield and the ester function could be easily reduced with DIBAL-H to provide **285**. Using Mitsunobu reaction for the preparation of 2-amino-6-chloropurine derivative **286** or thymine derivative **287** however, afforded only very low yields and therefore nucleobase assembly starting from amine **270** had to be employed for the preparation of these compounds.

Exact conformation of the pseudosugar part as well as its position on the puckering was determined using DFT calculations. This calculation was performed by Martin Dračínský, PhD and revealed, that the phase angle of the North analogues' puckering is $P = 22°$, which corresponds to the ^{3}E configuration.

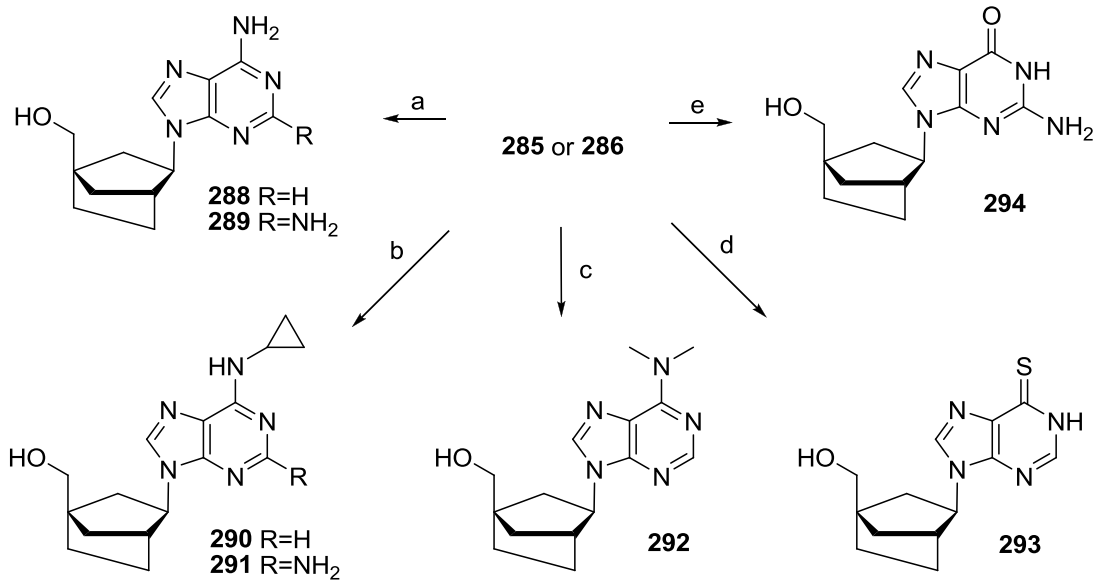


Scheme 38. a) PPh_3, DIAD, 6-chloropurine, THF, reflux, 5 h, 67%; b) DIBAL-H, DCM, -78°C, 45 min, 72% ; c) 4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 69% d) 2-amino-4,6-dichloro-5-formamidopyrimidine, DIPEA, EtOH-H_2O, MW, 140°C, 1 h, 83%; e) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100°, 3 h, 2. Dowex 50W (H^+), dioxane, 100°C overnight, 69%.



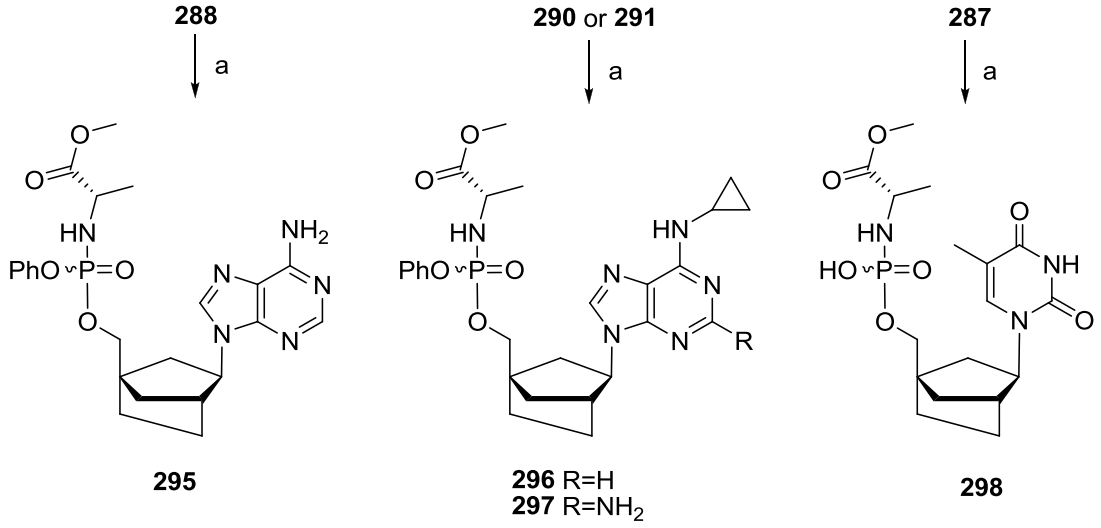
Picture 1. Computer generated model of compound **289**.

The C-6 position of purines **285** and **286** was derivatized to obtain a diverse spectrum of compounds which might provide interesting leads on the structure-activity relationship. Apart from obvious adenosine **288**, and guanosine **294** analogues, I have also prepared diaminopurine derivative **289**, 6-cyclopropylamino derivatives **290** and **291**, 6-dimethylamino derivative **292** and 6-thio derivative **293**.



Scheme 39. a) NH_3, EtOH, MW, 120°C, 30 min, 67% for **288**, 95% for **289**; b) cyclopropylamine, EtOH, MW, 140°C, 30 min, 80% for **290**, 83% for **291**; c) dimethylamino dimethylcarbamate, 24 h, 69% d) thiourea, EtOH, 105°C, 12 h, 77%; e) TFA, H_2O, 24 h, 60%.

From the adenosine derivative **288**, 2-amino-6-cyclopropylamino derivative **291** and thymidine analogue **287**, phosphoramidate prodrugs **295**, **296** and **297** have been prepared.



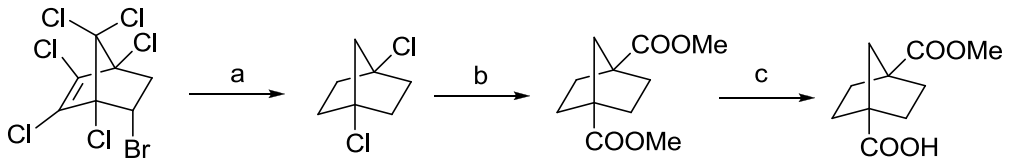
Scheme 40. a) *t*-BuMgCl, phenylmethoxyalaninyl phosphochloridate, THF, 3 d, 59% for **295**, 38% for **296**, 55% for **297**, 29% for **296**.

3.4. Synthesis of carbocyclic nucleoside analogues locked in East conformation

Analogues locked in East conformation are based on a 1,4-disubstituted, so called "double-bridgehead", norbornane. While some literature procedures leading to such substituted precursors are known, in my hands two of these described routes proved irreproduceable or afforded only very low yields. As in the case of North analogues, the nucleobase was built-up on a suitable amine precursor, followed by nucleophilic derivatization of the purine C-6 position and finally the preparation of phosphoramidate prodrugs from four nucleoside analogues.

3.4.1. Preparation of substrates suitable for the nucleobase introduction

Wilcox and Leung described[129] a method for carboxylic moiety introduction to both bridgehead positions starting from dichloride **300** and distinguishing them afterwards by careful saponofication of the diester **301**. Our attempts to prepare **300** started from readily available **299**, which was prepared from **220a** using Hunsdiecker reaction. The previously described removal of halogen atoms leading to the dichloride **300**,[130] however, was unsuccessful, and led to black tars in which the product was present (GC-MS), but could not be isolated in reasonable quantity.

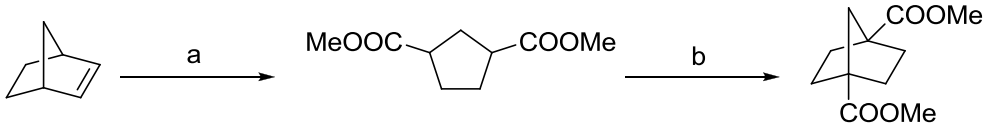


299 **300** **301** **302**

Scheme 41. a) 1. Zn, AcOH, 2. RaNi, H_2, KOH; b) 1. Li, CO_2, 2. CH_2N_2; c) KOH.

Della and Tsanaktsidis described a synthesis based on alkylation of dicarboxylate **304** with 1-bromo-2-chloroethane.[131a] Although this method has been used since then by other authors[131b] and I carefully followed the original formula, I was unable to

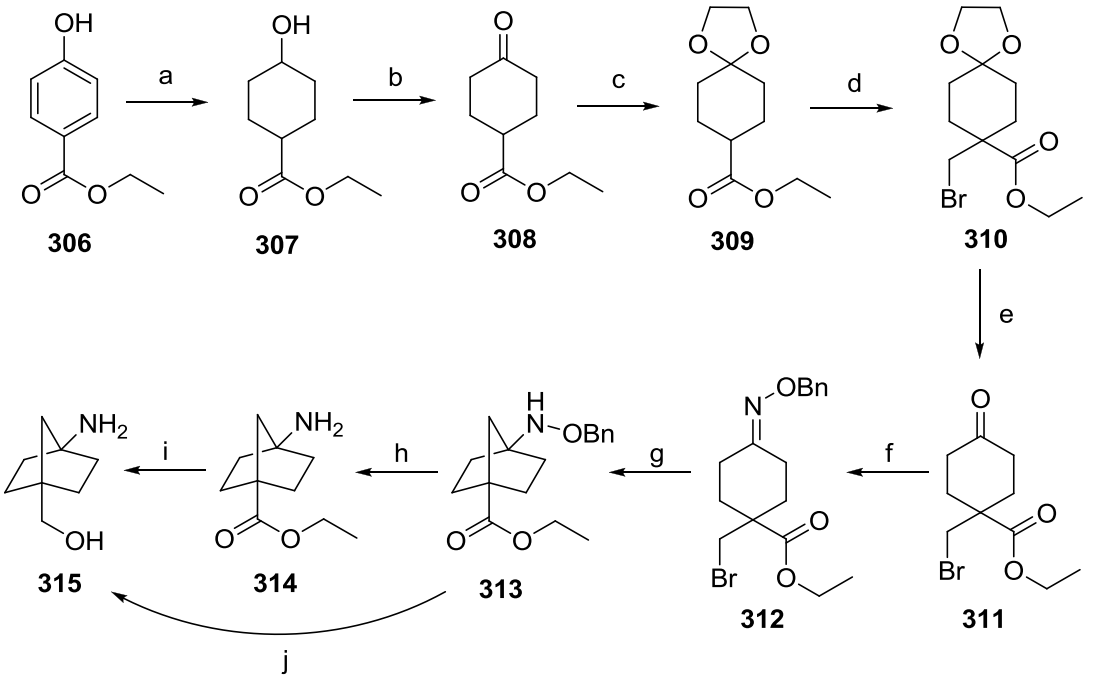
achieve yields higher than 10%. Optimization experiments with different reagents (1,2-dibromoethane, ethyleneglycol dimesylate instead of 1-bromo-2-chloroethane and lithium 2,2,6,6-tetramethylpiperidine instead of LDA) did not provide better results and with such low yields at the beginning of a long synthetic route, this approach was abandoned as well.



303 **304** **305**

Scheme 42. a) 1. $RuCl_3$, $NaIO_4$, 2. CH_2N_2; b) LDA, 1-bromo-2-chloroethane.

Fruitful was the third attempt to approach the double-bridgehead norbornanes. Della and Knill described the radical ring-closure reaction of benzylated oxime **312** using tributyl tinhydride and AIBN as a radical initiator.[132] **312** could be obtained in 6 simple steps from *p*-hydroxy ethylbenzoate **306**. The outline of the radical reaction had to be modified to provide acceptable yields (exact procedure described by authors afforded only cca 20% of product). Instead of dropwise addition of Bu_3SnH-AIBN solution to a refluxing solution of the substrate, I simply added AIBN all at once to a refluxing mixture of substrate and Bu_3SnH and the yield rose to 49%. Although originally I reduced of the hydroxylamine and the ester function of **313** in two steps, by using a modified version of borane reduction described in the literature[133] I was able to reduce both these functions in one reaction step with excellent yield of amine **315**.

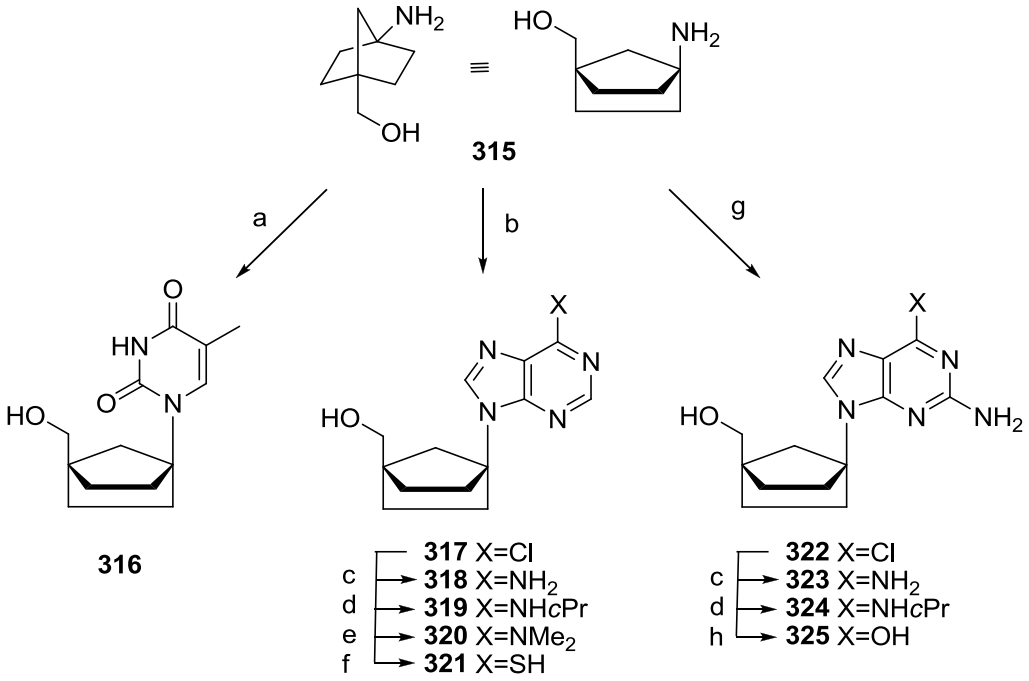


Scheme 43. a) Rh/Al_2O_3, H_2 (10 atm), EtOH, 48 h, 96%; b) PDC, DCM, 24 h, 86%; c) ethylene glycol, TsOH (cat.), benzene, reflux, 6 h, 94%; d) LDA, THF, HMPA, CH_2Br_2, -78°C to RT, 2 h, 70%; e) acetone, H_2SO_4 (cat.), overnight, 86%; f) O-benzylhydroxylamin hydrochloride, pyridine, EtOH, overnight, 87%; g) Bu_3SnH, AIBN, toluene, reflux, 5 h, 49%; h) $Pd(OH)_2/C$, H_2 (60 atm), MeOH, 24 h, 85%; i) $LiAlH_4$, THF, reflux 5 h, 67%; j) BH_3-THF, diglyme, 110°C, 24 h, 95%.

3.4.2. Nucleobase introduction, modifications of the purine nucleobase and preparation of phosphoramidate prodrugs

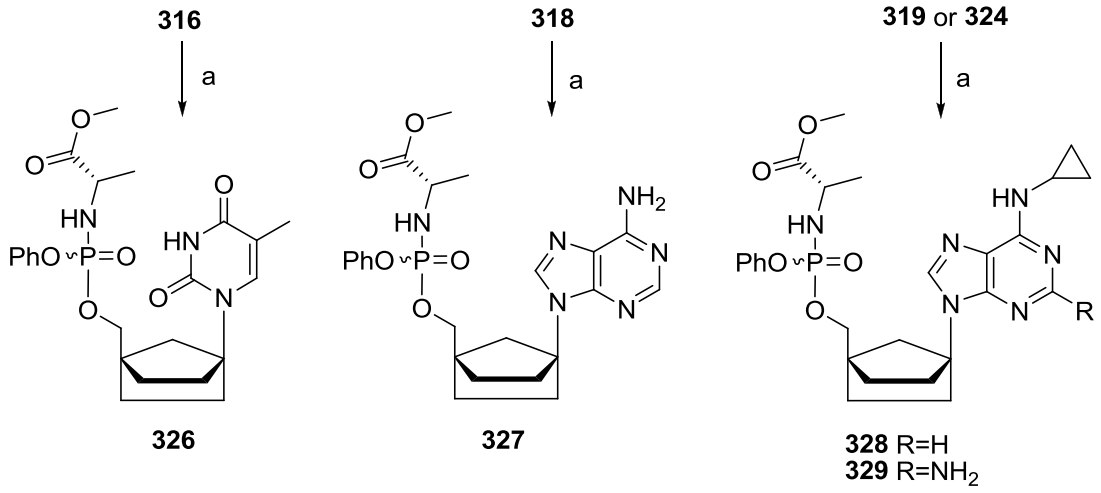
Nucleobase construction on the amino group of **315** smoothy provided derivatives **316**, **317** and **318**. Derivatization of the C-6 position of the purine heterocycle was performed under standard conditions, with the preparation of dimethylamino species **320** performed according to the method described by Čechová *et. al.*[122]

Exact conformation of the East derivatives was determined using X-ray diffraction and DFT calculation of compound **320**. The phase angle of the puckering is $P = 90°$, which corresponds to the envelope conformation ^{O}E. X-ray analysis was performed by Blanka Klepetářová, PhD, DFT calculation was performed by Martin Dračínský, PhD.

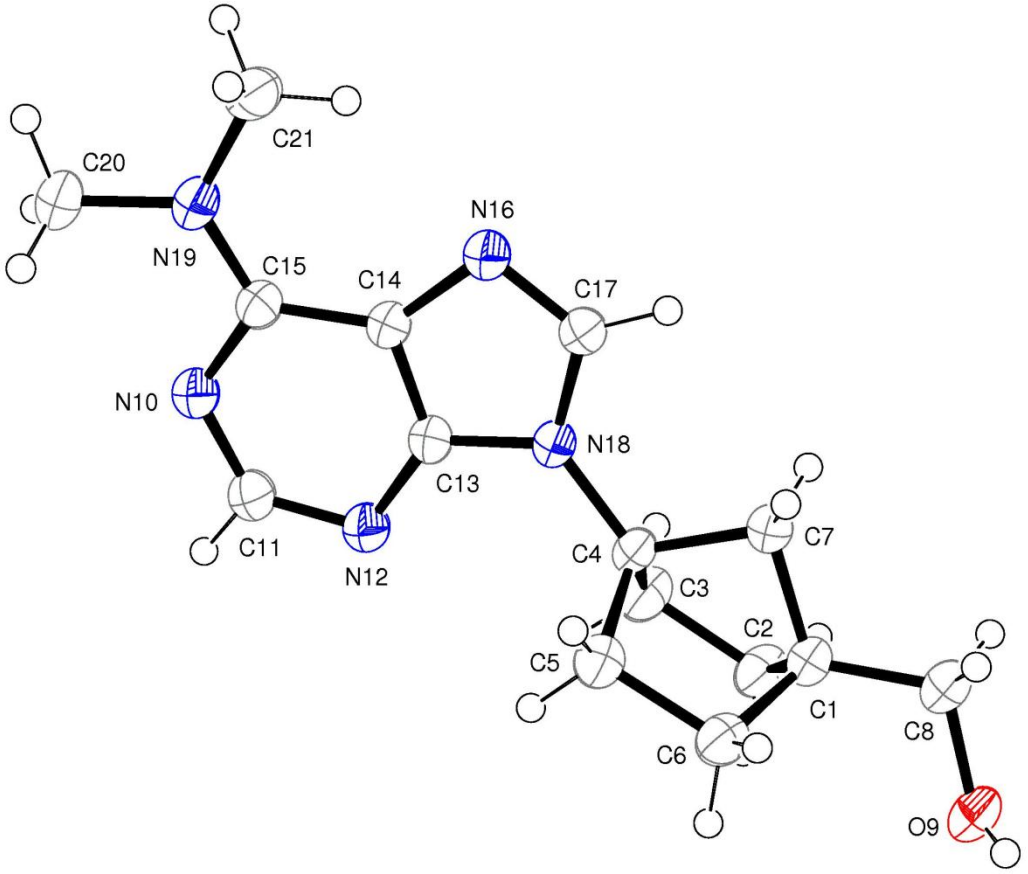


Scheme 44. a) 1. Ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100°, 3 h, 2. Dowex 50W (H^+), dioxane, 100°C overnight, 62%; b) 4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 60%; c) NH_3, EtOH, MW. 120°C, 30 min, 91% for **318**, 65% for **323**; d) cyclopropylamine, EtOH, 140°C, 30 min, 91% for **319**, 80% for **324**; e) DMF, MW, 200°C, 2 min, 87%; f) thiourea, EtOH, 105°C, overnight, 81%; g) 2-amino-4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 80%; h) TFA, H_2O, overnight, 69%.

Phosphoramidate prodrugs of **316**, **318**, **319** and **324** were obtained using standard conditions of *t*-BuMgCl and phenyl methoxyalaninyl phosphochloridate.



Scheme 45. a) *t*-BuMgCl, phenyl methoxyalaninyl phosphochloridate, THF, 3 d, 39% for **326**, 57% for **327**, 28% for **328**, 64% for **329**.



Picture 2. X-ray crystal structure of compound **320**.

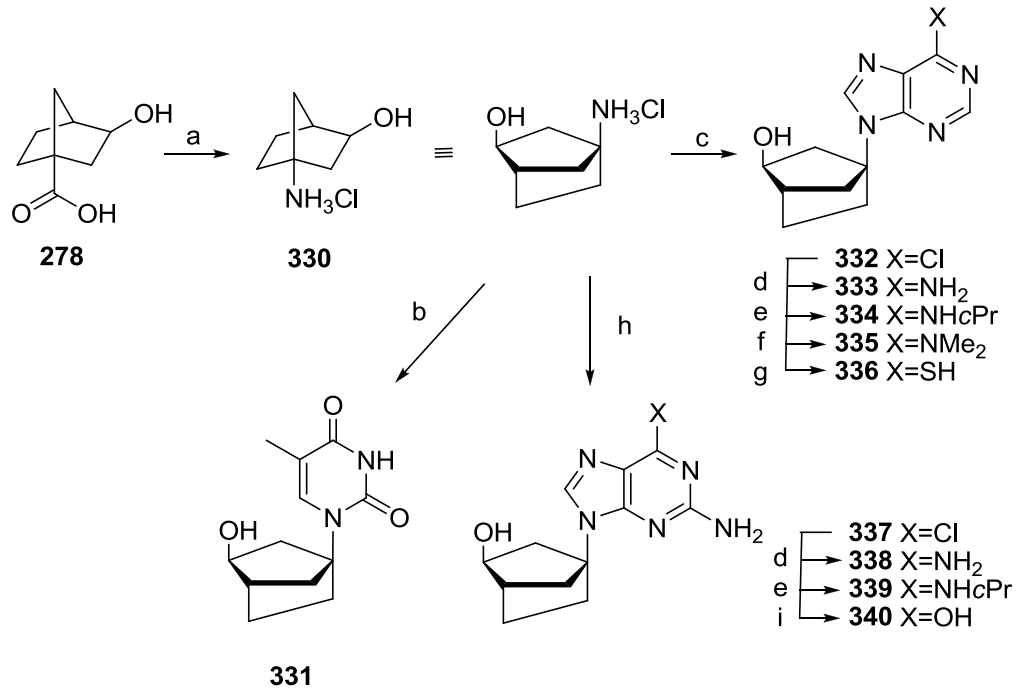
3.5. Synthesis of carbocyclic nucleoside analogues locked in South conformation

The pseudosugar part of the South derivatives is, much like in their North counterparts, a norbornane substituted in positions C-1 and C-3. Due to this similarity, same precursors were employed in their synthesis. In these compounds the nucleobase is in the C-1 position (bridgehead) of the norbornane bicycle and so the nucleobase has to be constructed on an amino group containing molecule. Introduction of an *exo* hydroxymethyl group to the C-3 position proved to be a very challenging task, for it would have required purchasing a high pressure instrument for reactions using synthesis gas. Therefore I decided to substitute this C-3 hydroxymethyl with a phosphonate functionality attached to a secondary hydroxyl group.

It should be noted that some of the compounds reported in this chapter (derivatives with a ketone or an *endo* hydroxyl in the position C-3) were aimed at the Coxsackie virus B3, much like compounds described in the Chapter 3.6. (Synthesis of N-9 alkylated 6-chloropurines and N-1 alkylated thymines as potential anti-Coxsackie agents). For the clarity and coherence of the text, which concerns synthesis more then biological activity, they are included here.

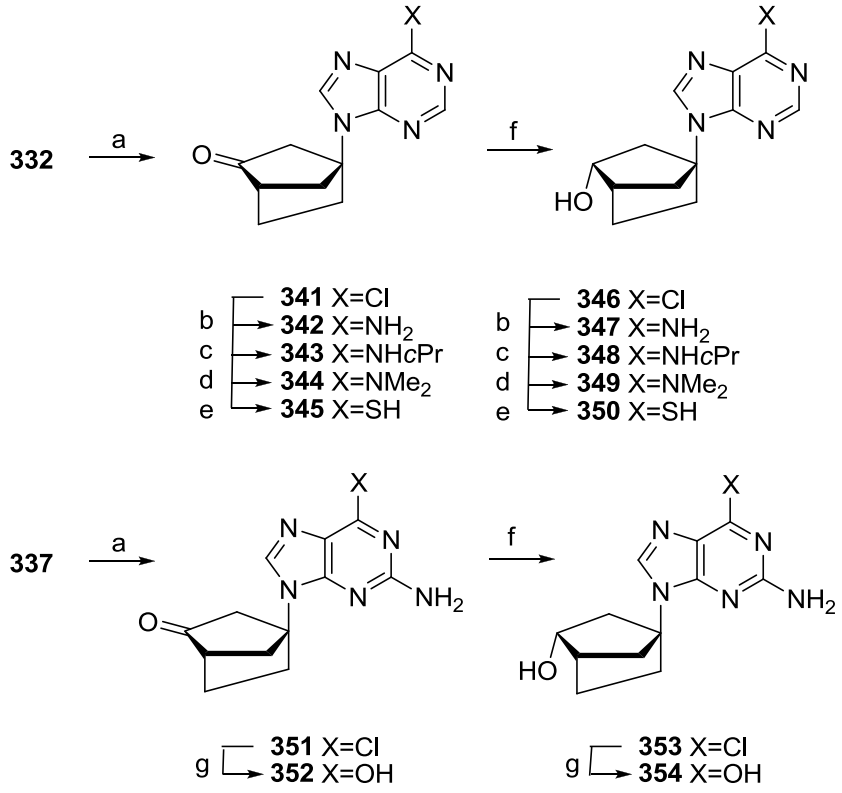
3.5.1. Amine substrate, nucleobase introduction and purine derivatization

Amine **330** was prepared by means of the Curtius rearrangement from carboxylic acid **278**. On the amino group of **330**, the thymine, 6-chloropurine and 2-amino-6-chloropurine was constructed affording compounds **331**, **332** and **337**, respectively.



Scheme 46. a) 1. ClCOOEt, TEA, acetone, 0°C, 1 h, 2. NaN_3, H_2O, 0°C, 1h, 3. Dioxane, HCl, reflux, 5 h, 74%; b) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100°, 3 h, 2. Dowex 50W (H^+), dioxane, 100°C overnight, 61%; c) 4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 58%; d) NH_3, EtOH, 120°C, 30 min, 83% for **333**, 83% for **338**; e) cyclopropylamine, EtOH, MW, 140°C, 30 min, 88% for **334**, 76% for **339**; f) dimethylamino dimethylcarbamate, 24 h, 86%; g) thiourea, EtOH, 105°C, overnight, 76%; h) 2-amino-4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 63%; i) TFA, H_2O, 24 h, 56%.

The C-3 hydroxy group of **332** and **337** was inverted using the standard oxidation-reduction procedure and although reduction of **341** to **346** proceeded smoothly (less than 2% of **332**), reduction of **351** to **353** yielded a mixture of **337** and **353** (6:1) which was difficult to separate. The chlorine atom in the C-6 position of the purine nucleobase of all these six compounds was nucleophilically exchanged for a variety of substituents and thus expanded our library of nucleoside analogues and related compounds.

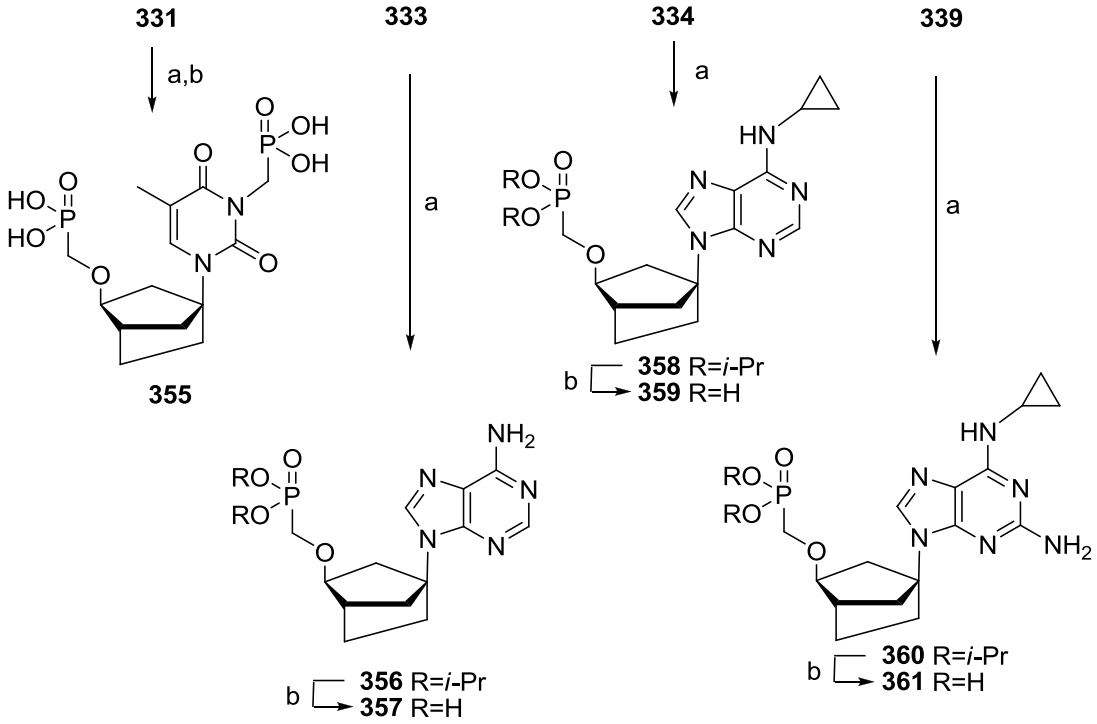


Scheme 47. a) PDC, DCM, 7 d, 82% for **341** or PDC, DMF, 12 h, 56% for **351**; b) NH_3, EtOH, 120°C, 30 min, 77% for **342**, 70% for **347**; c) cyclopropylamine, EtOH, MW, 140°C, 30 min, 88% for **343**, 77% for **347**; d) dimethylamino dimethylcarbamate, 24 h, 86% for **344**, 86% for **349**; e) thiourea, EtOH, 105°C, overnight, 76% for **345**, 89% for **350**; f) $NaBH_4$, MeOH, 5 h, 89% for **346**, 51% for **353**; g) TFA, H_2O, 24 h, 86% for **352**, 62% for **354**.

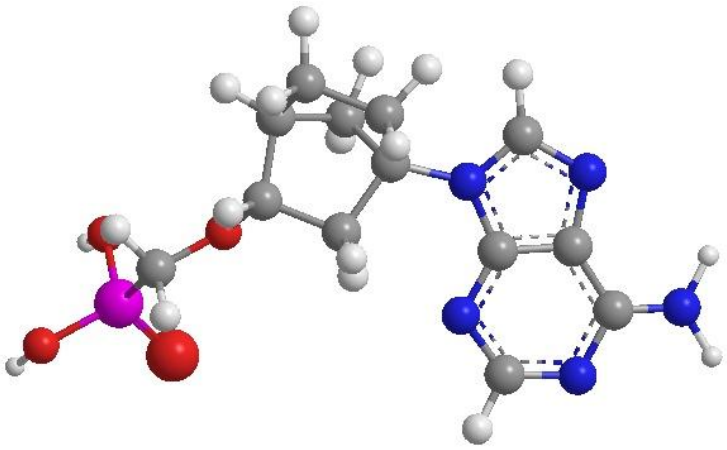
3.5.2. Synthesis of phosphonates

Phosphonate functionality was introduced to **333**, **334** and **339** using tosylmethanphosphonate as the alkylating agent. Use of $(t\text{-BuO})_2Mg$ as a base and DMF as a solvent afforded significantly better yields than the use of *t*-BuONa in THF.

Using DFT calculations it was determined that the conformation of the pseudosugar in this case is ^{2}E, which corresponds to the phase angle P = 160° on the pseudorotation cycle. These calculations were performed by Martin Dračínský PhD.



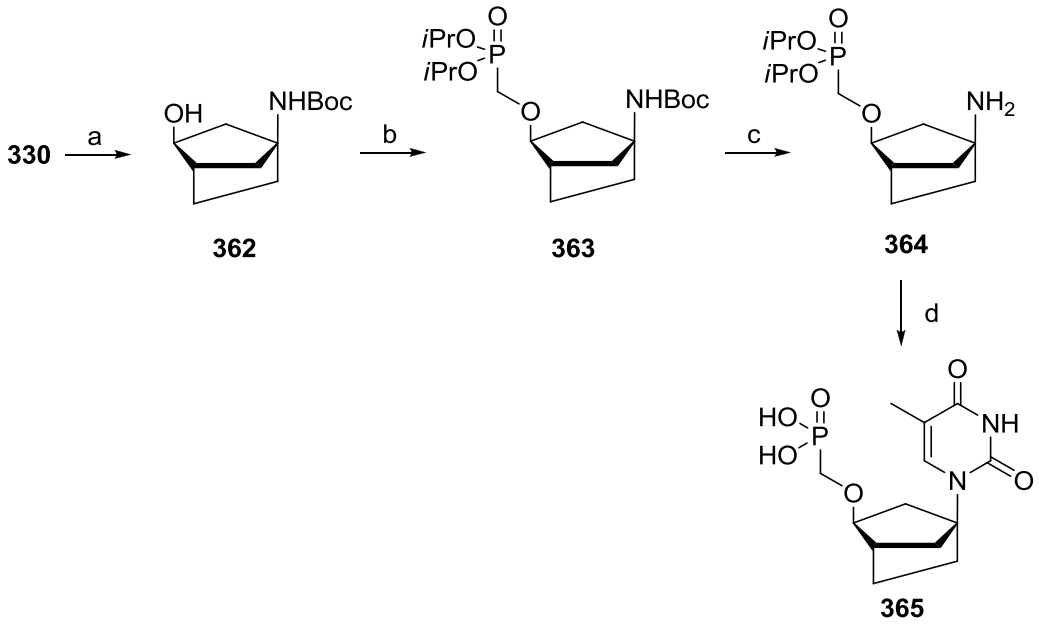
Scheme 48. a) $(t\text{-BuO})_2Mg$, $TsCH_2P(O)(Oi\text{-Pr})_2$, DMF, 60°C, 48 h, 89% for **356**, 81% for **358**; 58% for **360**, b) TMSBr, DCM, 24 h, 60% for **355**; 81% for **357**; 58% for **359**, 60% for **361**.



Picture 3. Computer generated model of compound **357**.

Direct alkylation of the thymine-based compound **331** afforded a product alkylated on both the hydroxyl group and the N-3 position of the thymine nucleobase. Therefore the phosphonate moiety was introduced first to a Boc-protected **330** and the thymine was constructed afterwards. An interesting feature of this reaction is the fact that during the Dowex 50 (H^+) catalyzed ring-closure reaction

of the thymine nucleobase, the phosphonate diester was converted to a free phosphonate which then had to be isolated on C-18 reverse phase.



Scheme 48. a) Boc_2O, DIPEA, DCM, overnight, 89%; b) (*t*-BuO)$_2$Mg, $TsCH_2P(O)(O$*i*-Pr$)_2$, DMF, 60°C, 48 h, 58%; c) TFA, DCM, 2 h, 56%; d) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100°, 3 h, 2. Dowex 50W (H^+), dioxane, 100°C, 12 h, 43%.

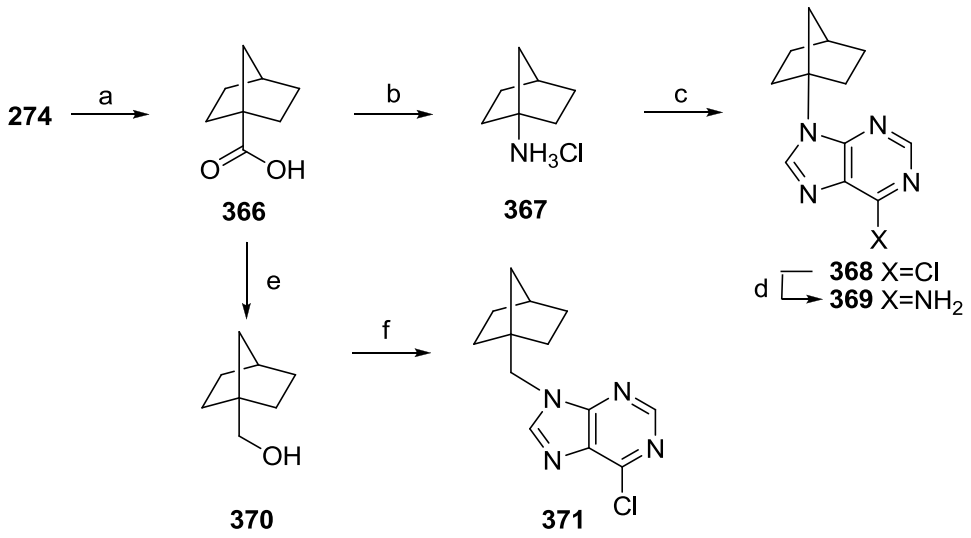
3.6. Synthesis of N-9 alkylated 6-chloropurines and N-1 alkylated thymines as potential anti-Coxsackie agents

The discovery of anti-CVB3 activities of N-9 substituted 6-chloropurines by Šála[97f-h] led our team to continue searching for compounds of similar structure that would possess even higher antiviral potency. The most active compounds were mentioned in chapter 1.3.6. and the resemblance of their norbornane core with some of the synthetic intermediates listed in the three previous chapters suggest that the synthesis of compounds based on bridgehead substituted bicyclic skeletons is potentially facile and may result in interesting hits in antiviral screening against Coxsackievirus B3 and/or other viruses.

3.6.1. Compounds based on bridgehead substituted norbornane

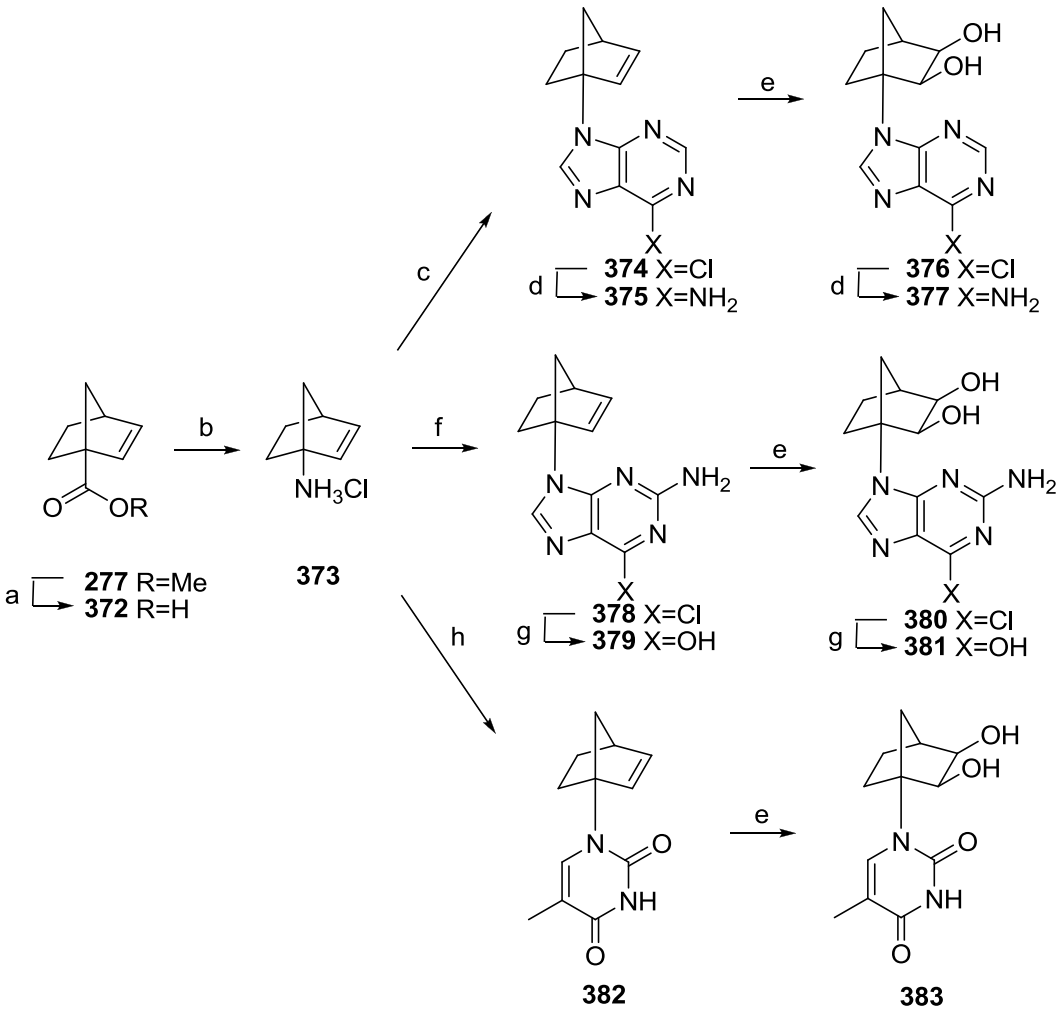
Removal of the bromine atom of **274** with hydrogenolysis provides acid **366**, which can be easily transformed to 1-norbornylamine hydrochloride **367** *via* Curtius rearrangement. 6-Chloropurine construction provides final 6-chloro-9-(1-norbornyl)-9*H*-purine **368**, which was further modified to an adenine derivative **369**.

Reduction of the carboxylic function of **366** with lithium aluminium hydride affords alcohol **370**,[134] which was easily transformed into **371** via Mitsunobu reaction.



Scheme 49. a) $Pd(OH)_2/C$, H_2 (5 atm), NaOH, H_2O-MeOH, 12 h, 75%; b) 1. ClCOOEt, TEA, acetone, 0°C, 1 h, 2. NaN_3, H_2O, 0°C, 1 h, 3. toluene, HCl, reflux, 5 h, 50%; c) 1. 5-amino-4,6-dichloropyrimidine, TEA, EtOH, 105°C, 6 d, 2. $CH(OEt)_3$, HCl (cat.), 5 d, 61%; d) NH_3, EtOH, 120°C, 20 min, 83%; e) $LiAlH_4$, THF, reflux, 2 h, 67%; f) 6-chloropurine, PPh_3, DIAD, THF, overnight, 78%;

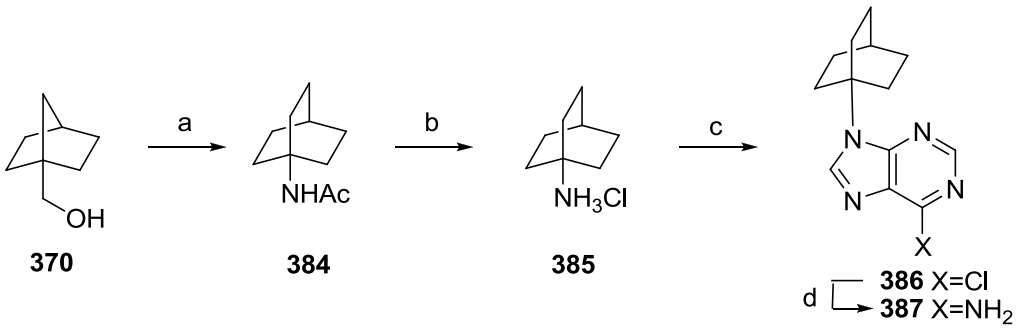
Analogous unsaturated compounds can be easily prepared from another intermediate previously used in the synthesis of North-conformation derivatives. Ester **277** was saponified and resulting carboxylic acid **372** transformed to amine **373** *via* Curtius rearrangement. Compounds **374**, **378** and **382** were prepared using nucleobase assembly protocol and the double bond of these unsaturated compounds was then subjected to *cis*-hydroxylation affording diols **376**, **380** and **383.** C-6 position of both purine nucleobases was derivatized, with the 6-chloropurine being ammonolyzed to adenine and 2-amino-6-chloropurine being hydrolyzed to guanine under acidic conditions.



Scheme 50. a) NaOH, H_2O-MeOH, reflux, 1 h, 97%; b) 1. ClCOOEt, TEA, acetone, 0°C, 1 h, 2. NaN_3, H_2O, 0°C, 1 h, 3. toluene, HCl, reflux, 5 h, 79%; c) 1. 5-amino-4,6-dichloropyrimidine, TEA, EtOH, 105°C, 6 d, 2. $CH(OEt)_3$, HCl, 5 d, 40% d) NH_3, EtOH, 120°C, 20 min, 76% for **375**, 64% for **377**; e) OsO_4, NMMO, dioxane -H_2O, 48 h, 78%, for **376**, 85% for **380,** 78% for **383**; f) 2-amino-4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 57%; g) TFA, H_2O, 48 h, 81% for **379**, 85% for **381**; h) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl] carbamate, dioxane, 100°, 3 h, 2. Dowex 50W (H^+), dioxane, 100°C, 12 h, 58%.

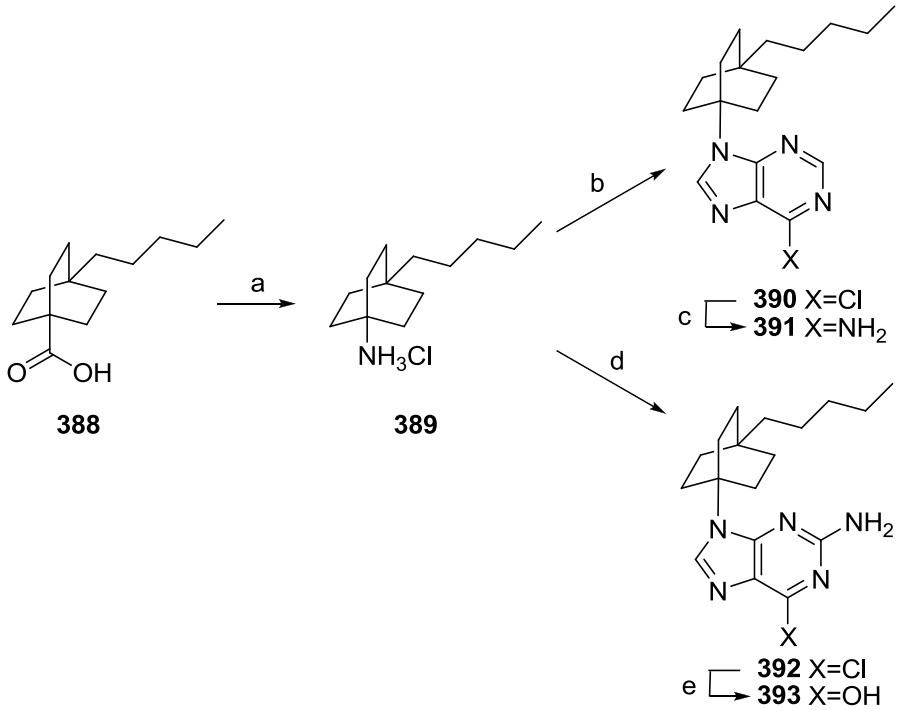
3.6.2. Compounds based on bridgehead substituted bicyclo[2.2.2]octane

Ritter reaction of the 1-hydroxymethyl norbornane **370** connected with the skeleton rearrangement, using acetonitrile as a source of nitrogen affords **384**, acetylated 1-bicyclo[2.2.2]octylamine.[134] After the amino group is deprotected, the 6-chloropurine nucleobase is built-up yielding **386**.



Scheme 51. a) Oleum, MeCN, -20°C, 2 h, 94%; b) HCl, reflux, 10 h, 90%; c) 1. 5-amino-4,6-dichloropyrimidine, TEA, EtOH, 105°C, 6 d, 2. $CH(OEt)_3$, HCl (cat.), 5 d, 65%; d) NH_3, EtOH, 120°C, 20 min, 83%;

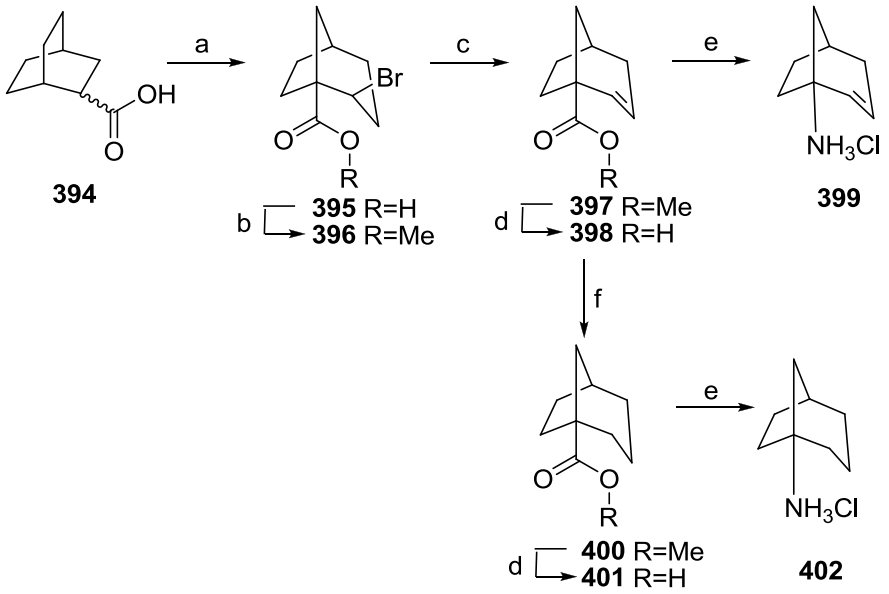
In order to explore increased lipophilicity of the bicyclic skeleton, I have prepared compounds **390**-**393**, which are based on 4-pentylbicyclo[2.2.2]octane. Using the same methodology as in Chapter 3.6.2., commercially available carboxylic acid **388** was transformed to amine **389** *via* Curtius rearrangement and on this amino group, purine nucleobases were constructed and subsequently modified.



Scheme 52. a) 1. ClCOOEt, TEA, acetone, 0°C, 1 h, 2. NaN_3, H_2O, 0°C, 1 h, 3. dioxane, HCl, reflux, 5 h, 79%; b) 1. 5-amino-4,6-dichloropyrimidine, TEA, *n*-BuOH, MW, 160°C, 4 h, 2. $CH(OEt)_3$, HCl (cat.), 3 d, 49%; c) NH_3, 70°C, 12 h, 86%; d) 2-amino-4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 2 h, 57%; e) TFA, H_2O, 48 h, 72%.

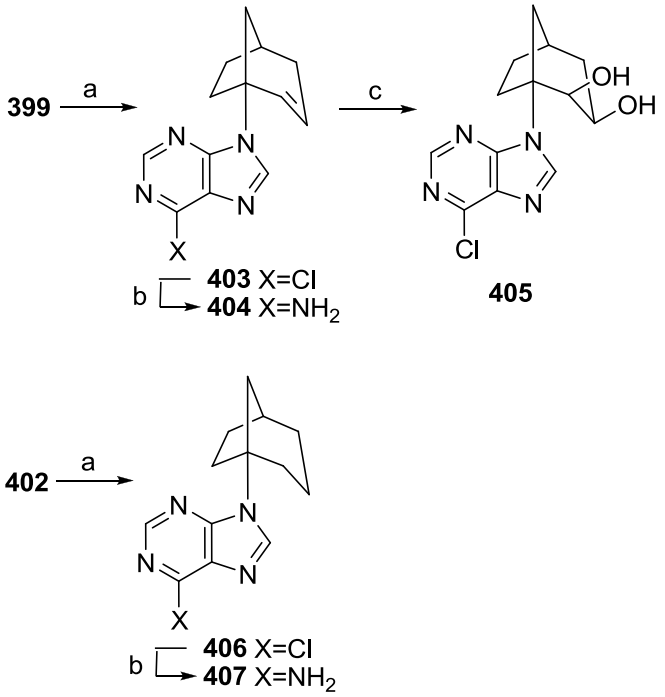
3.6.3. Compounds based on bridgehead substituted bicyclo[3.2.1]octane

Anti-Coxsackie activity of the compounds based on norbornane and bicyclo[2.2.2]octane led me to a search for other potentially interesting bicyclic motifs that can be implemented in the library of our compounds. Different layout of the bicyclic skeleton, bicyclo[3.2.1]octane, can be easily obtained using Hell-Volhard-Zelinski bromination of **394** - a substrate similar to **273** (chapter 3.3.1), which afforded bridgehead substituted 2-bromonorbornane.[135] The skeleton rearrangement in this case, however, proceeds differently and provides **395**, which is then used in reactions analogous to those described in the Schemes 35 and 50. After esterification of carboxyl group, the bromine atom is eliminated using DBU in DMF, followed by subsequent saponification of the ester function of **397** and finally the carboxylic acid is converted to amine **399** *via* the Curtius rearrangement. Saturated analogues are prepared in the same manner, only the double bond of **397** is hydrogenated prior to the saponification. It is worth mentioning that the described hydrogenolysis of the bromine atom of **395** under basic conditions[135b] gave only low yields and had to be substituted with hydrogenation of alkene **397**.



Scheme 53. a) Br_2, PCl_3 (cat.), 80°C, 8 h, 55%; b) CH_2N_2, Et_2O, 30 min, 99%; c) DBU, DMF, 80°C, overnight, 91%; d) NaOH, MeOH-H_2O, overnight, 93% for **398**, 53% for **401**; e) 1. ClCOOEt, TEA, acetone, 0°C, 1 h, 2. NaN_3, H_2O, 0°C, 1 h, 3. dioxane, HCl, reflux, 5 h, 73% for **399**; 83% for **402**; f) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, 12 h, 76%.

Using classical procedures, the 6-chloropurine nucleobase was constructed on amines **399** and **402** and double bond of **403** was *cis*-hydroxylated using osmium tetroxide.



Scheme 54. a) b) 1. 5-amino-4,6-dichloropyrimidine, DIPEA, *n*-BuOH, MW, 160°C, 8 h, 2. $CH(OEt)_3$, HCl (cat.), 2 d, 55% for **403**, 37% for **406**; c) NH_3, 70°C, 12 h, 79% for **404**, 43% for **407**; c) OsO_4, NMMO, dioxane-H_2O, 48 h, 59%.

3.7. Biological activities of prepared compounds

All final compounds were screened for antiviral activity against several different viruses. Although not all the results are available at the moment, some conclusions can be drawn even from the incomplete set of data. 6-Chloropurine and 2-amino-6-chloropurine derivatives were aimed mostly at the Coxsackievirus B3, while compounds containing "natural" nucleobases (adenine, guanine) or their modifications (N^6- alkylated adenines, diaminopurine, 2-amino-6-cyclopropylaminopurine) were employed in the general screening aimed at a set of viruses including HIV, HCV, influenza type A and B, Chikungunya virus and feline herpes virus (FHV-1). Antiviral screening was performed by our collaborators: Gilead Sciences (Foster City, CA, USA) and groups of Jan Balzarini and Johan Neyts (KU Leuven, Belgium).

Cytostatic activity of prepared compounds was evaluated (group of Helena Mertlíková-Kaiserová at IOCB, Prague) and guanine-based compounds were evaluated as potential inhibitors of hypoxanthine-guanine-xanthine-phosphoribosyl transferase, an enzyme that plays an important role in the metabolism of *Plasmodium*, a parasite that causes malaria[136] (group of Luke Guddat, University of Queensland, Brisbane, Australia).

3.7.1. Antiviral activities against Coxsackievirus B3

Coxsackieviruses belong to the Picornaviridae family, the genus Enteroviruses (together with Echovirus, Enterovirus, Rhinovirus and Poliovirus).[137] This small uncoated, (+)ssRNA virus with icosahedral capsid is one of the most common and important human pathogens, causing 10-15 milion symptomatic infections in the world every year.[138] Coxsackieviruses are further divided into types A and B according to observed pathogenicity in juvenile mice. 23 serotypes of group A (A1-22 and A24) and 6 serotypes of group B are recognized.

Coxsackieviruses of A type tends to infect skin and mucous membranes, causing mostly hand, foot and mouth disease, herpangina and hemorrhagic conjunctivitis. Coxsackievirus of type B infects mostly internal organs such as heart, pancreas and liver causing myocarditis, pericarditis and hepatitis. Serotype B4 has also been associated with the development of diabetes type 1.[137] Most common transmision is fecal-oral (contaminated food or water, contact with infected feces).

Although a vast majority of the symptomatic infections are not life-threatening, Coxsackievirus induced myocarditis or pericarditis can result in permanent heart damage or death. Also up to 50% of sudden death incidents are accounted for by this group of viruses.[139]

Anti-coxsackie agents are of great scientific interest, since there is no FDA approved therapy against infections caused by these viruses and there is also no available vaccination. Results of anti-CVB3 screening are listed in the Table 7.

Table 7. Results of anti-CVB3 screening.

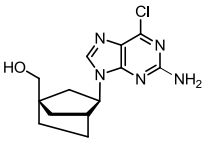
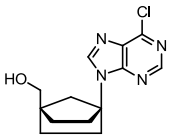
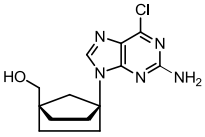
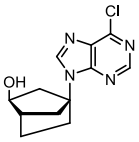
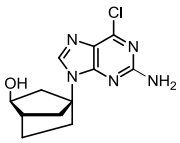
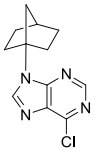
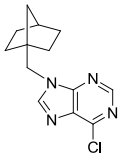
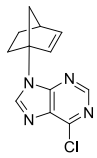
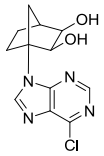
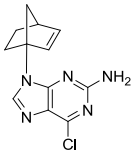
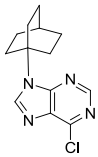
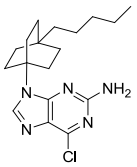
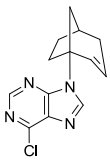
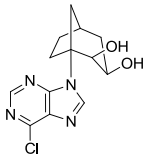
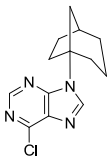
	Compound	EC_{50} [μM]	EC_{90} [μM]	CC_{50} [μM]
286		30.4	58.6	> 400
317		28.6	> 300	> 400
322		31.8	62.6	> 400
332		32.3	68.8	> 400
337		33.2	64.3	> 400
368		18.1	24.7	> 400

Table 7. Results of anti-CVB3 screening - continued.

Compound		EC_{50} [μM]	EC_{90} [μM]	CC_{50} [μM]
371		31.9	> 300	> 400
374		18.4	24.1	> 400
376		32.7	91.2	> 400
378		17.4	23.5	> 400
386		17.4	28	> 400
392		24.7	49.2	> 400
403		7.56	15.2	> 400
405		30.3	57.3	> 400
406		31.7	70	> 400

Although these results prove that N-9 alkylated 6-chloropurines generally possess interesting anti-CVB3 activity without any cytotoxicity, none of the prepared compounds, however, exerted activity comparable to structures **200** and **201** described by Šála et. al.[97g,h]

3.7.2. Antiviral activities against other viruses

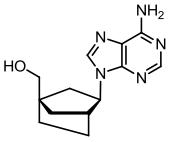
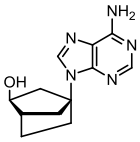
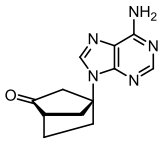
The results of the general screening was mostly disappointing. Although some compounds exerted certain activity against HIV or HCV, it mostly correlated with their cytotoxicity. This applies especially to the phosphoramidate prodrugs of North and East conformation derivatives and to phosphonates (South conformation derivatives). An interesting exception is compound **288**, which is active against both HIV-1 (EC_{50} = 100 ± 30 μM, CC_{50} > 400 μM) and HIV-2 (EC_{50} = 231 ± 66 μM, CC_{50} > 400 μM). Although this adenosine analogue is cca 5-fold less active compared to PMEA[140] used as standard, it must be stressed that it is a racemic mixture and it is well known that optical antipods usually greatly differ in biological activity.[141] One of the enantiomers could therefore be significantly more potent then the racemic mixture. Also it is very unusual for a conformationally locked carbocyclic nucleoside to be active without preceding phosphorylation.

Two interesting hits were recorded against the Chikungunya virus (**390** with EC_{50} = 13.8 μM, CC_{50} > 400 μM and **392** with EC_{50} = 12.3 μM, CC_{50} > 400 μM).

Compound **288** exerted some activity against Influenza A virus, subtype H1N1 (EC_{50} = 174 μM, CC_{50} > 400 μM), however such weak activity was not studied further.

Three compounds were also found active against feline herpes virus, their activities are listed in the Table 8.

Table 8. Results of screening for anti-FHV-1 activity.

Compound		EC_{50} [μM]	CC_{50} [μM]
288		65.2	> 400
333		69.3	> 400
342		34.9	> 400

3.7.3. Cytostatic activity and activity against HXGPRTase

For the cytostatic activity screening were employed following cell lines: L1210 (murine leukemia), HeLaS3 (cervical cancer), HL60 (human promyelocytic leukemia) and CCRF-CEM (human T-lymphoblastoids). None of the evaluated compounds exerted any elevated inhibition of the cell growth.

None of the compounds tested for the activity against HXGPRTase exerted any activity against this enzyme. Possible explanation might be that the compounds are either too large for the enzyme active site, or that it does not have enough polar groups to anchor in the active site properly.

4. Conclusion

The main goal of this work was to synthesize carbocyclic nucleoside analogues locked *via* an ethylene bridge in different conformations, and study the influence of the conformation on their biological activity. Apart from this main topic, It was also intended to employ the intermediates from these syntheses in the preparation of N-9 alkylated purines as direct analogues of 6-chloro-9-(2-norbornyl)-purine **200**, a potent inhibitor of Coxsackievirus B3. These products were meant to become a part of greater library of norbornane-based compounds, which our research team has built over the last decade. Their knowledge might help us better understand the structure-activity relationship of this type of molecules.

I have developed and optimized synthetic strategies leading to 1,3- and 1,4-disubstituted norbornane cores and used these compounds in the preparation of novel purine- and thymine-based carbocyclic nucleoside analogues locked in North, East and South conformation. I have also prepared a small library of compounds with several different substituents introduced to the C-6 position of the purine nucleobase.

Synthesis of the 1,3-disubstituted norbornane precursor is based on the Hell-Volhard-Zelinski bromination of norbornane-2-carbocylic acid, which allows the introduction of a carboxylic functionality into the bridgehead (C-1) position. To introduce the C-3 substituent I have employed regio- and stereoselective oxymercuration reaction, which provided the key intermediate **278** (3-hydroxynorbornane-1-carboxylic acid), which then served as a stepping stone in the syntheses of both North and South conformation derivatives.

Synthesis of double bridgehead substituted norbornane as a suitable precursor in the preparation of the East derivatives was accomplished using a slightly modified literature procedure of radical ring-closing reaction mediated by Bu_3SnH and using AIBN as the reaction initiator. Although this multistep synthesis was very time

consuming, attempts to obtain a similar precursor using alternative approaches, although described in literature, were unsuccessful.

In all cases the 6-chloropurine, 2-amino-6-chloropurine or thymine nucleobase was constructed on a corresponding amine precursor, and subsequent derivatization of the C-6 position was performed using standard procedures employing various nucleophiles. Phosphoramidate prodrugs (North and East derivatives) as well as the phosphonate functionality (South derivatives) were introduced *via* Grignard reagent mediated phosphochloridate introduction and alkylation with tosylmethanphosphonate, respectively.

As a part of our long-term search for potent anti-Coxsackie agents I have prepared a number of 6-chloropurines substituted in the position N-9 with three different bicyclic cores - bicyclo[2.2.1]heptane (norbornane), bicyclo[2.2.2]octane and bicyclo[3.2.1]octane. Although this project, mostly using literature procedures, did not include any synthetic challenge, we have obtained a great deal of valuable information on biological activities of this type of compounds filling further gaps in our systematic work.

In order to simplify access to norbornane-based carbanucleoside analogues I devised two new synthetic methodologies. The first methodology is the microwave assisted Diels-Alder reaction of dicyclopentadiene or polychlorinated cyclopentadienes with several simple dienophiles leading to variously substituted norbornenes. These bicyclic skeletons represent invaluable precursors in organic chemistry (e.g. natural products, carbanucleosides) and their derivatives have vast applicability in industry (e.g. plasticizers, flame retardants, lubricants, fragrances). I have succesfully implemented this technique in my work to synthesize starting materials for my syntheses.

The second methodology is the modified Traube synthesis, a reaction in which purine nucleobase is constructed on the amino group of a substrate using various pyrimidine synthons. The devised methodology represents a significant improvement in simplicity, yields and reaction speed over previously described methods and proved advantageous for the nucleobase introduction to my bicyclic precursors.

All compounds were screened for antiviral and cytostatic activities in our collaborators' facilities (Gilead Sciences, CA, USA, groups of Jan Balzarini and Johan Neyts in KU Leuven, Belgium and group of Helena Mertlíková-Kaiserová at IOCB, Prague). Although acquired results of the antiviral screening did not fulfill our

expectations (majority of compounds did not exert significant activities against targeted viral strains or the recorded activity largely correlated with their cytotoxicity), several interesting hits, especially against Coxsackievirus B3, were recorded. Low antiviral potency of nucleoside analogues together with the fact that some of the compounds have not yet been evaluated for their activity makes it impossible to determine any relationship between the pseudosugar conformation and biological activity.

5 Experimental section

5.1. Used equipment and general remarks

Reagents and solvents were purchased and used as received, or prepared according to published procedures.

NMR spectra were recorded on Bruker Avance I 500 (^{1}H at 500 MHz, ^{13}C at 125.8 MHz) and Bruker Avance II 600 (^{1}H at 600 MHz, ^{13}C at 150 MHz) spectrometers using DMSO-d_6 or $CDCl_3$ as a solvent and using solvent signal as a reference. Chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively. All structures were confirmed and ^{1}H and ^{13}C signals were assigned by a combination of 1D and 2D NMR (H,H-COSY, H,C-HSQC, H,C-HMBC, ROESY) techniques. Standard pulse programs from the library of the spectrometer were used; gradient selection was used in the 2D experiments.

Mass spectra were measured using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix), EI (electron energy 70 eV) or electrospray ionization (ESI). HRMS analyses of pure compounds was conducted on an LTQ Orbitrap XL instrument (Thermo Fisher Scientific), using ESI. GC-MS analyses were performed on a 6890N gas chromatograph (Agilent, Santa Clara, CA, USA) equipped with a Phenomenex ZB-5 HT capillary column (30 m × 0.25 mm, film thickness 0.25 mm); temperature: 60 °C (2 min), then 10 °C/min to 320 °C (10 min); coupled to a 5975B quadrupole mass spectrometer.

HPLC-MS analyses (Chapter 3.2., measurements performed by Ing. Eva Zborníková) were carried out on Waters 600 controller on RPC18 column (4.6 x 100 mm, 3 μm) and analytes were identified by UV (Waters 2998) and MS (Waters 3100). Elution was carried out with aqueous acetonitrile gradient. A = 25 mM NH_4Ac, B = 25 mM NH_4Ac in 50% MeCN, C = 100% MeCN; t_{0min} 95% A - 5% B, t_{6min} 100% B, t_{16min} 100% C; flow 1mL / min. Concentration of products in

reaction mixtures was determined by calibration on an external standard on the same column, analytes were identified by UV (Waters 2996). Elution was carried out with aqueous acetonitrile gradient. A = 100 mM TEAA, B = 100 mM TEAA in 50% MeCN, C = 100% MeCN. t_{0min} 95% A - 5% B, t_{6min} 100% B, t_{16min} 100% C; flow 1mL / min.

Elemental analyses were measured on Perkin Elmer CHN Analyzer 2400, Series II Sys (Perkin Elmer, Norwolk, CT U.S.A.) or on SPECTRO iQ II (Spectro Analytical Instruments, Germany).

Melting points are uncorrected and were determined on Büchi Melting Point B-540 apparatus.

Microwave syntheses were carried out in a CEM Discover instrument with a single-mode cavity and focused microwave heating (microwave power supply 0–300 W, 1W increments, IR temperature sensor, sealed vessel mode, pressure range 0–20 bar, 10 or 60 mL vials).

Column chromatography was performed on a 40-60 μm silica gel using ISCO flash chromatography system or standard glass columns.

Purity of all prepared compounds was higher than 98% unless stated otherwise.

Geometry of studied compounds (**289**, **320**, **357**, Chapters 3.3., 3.4. and 3.5., calculations performed by Martin Dračínský, PhD.) was optimized with DFT method using B3LYP functional[142] and 6-31G(d,p) basis set. Substituents on the purine moiety and on hydroxyls were replaced by hydrogen atoms before the optimization. Gaussian 09 program package was used for the geometry optimization.[143] The pseudorotation phase angle P and amplitude of pucker Φ_m were calculated to minimize the differences between the ring torsion angles ($\nu 0 - \nu 4$) found in the geometry optimized structures and the torsion angles calculated according to the equation:[144] $\nu_j = \Phi_m \times \cos[P + 144^o \times (j-2)]$ (j = 0, 1, 2, 3, 4)

5.2. General methods for common reactions

A: Construction of a 6-chloropurine or a 2-amino-6-chloropurine nucleobase using formylated pyrimidine reagents

To a solution of the amine substrate (1 mmol) in a suitable solvent (5 mL), 4,6-dichloro-5-formamidopyrimidine (230 mg, 1.2 mmol) or 2-amino-4,6-dichloro-5-formamidopyrimidine (250 mg, 1.2 mmol) and DIPEA (348 μL, 2 mmol when starting from a free amine substrate, 523 μL, 3 mmol when starting from a hydrochloride, substrate containing free acid group or phosphonate diester) was added and the reaction mixture was heated in a sealed vessel on corresponding temperature for the specified time. Purification was performed either by crystallization (precipitation of insoluble product from the reaction mixture), flash chromarography on silica gel (hexane - ethyl acetate or ethyl acetate - methanol gradient) or HPLC (water - acetonitrile or 50 mM TEAB - acetonitrile gradient). Chromatographically obtained products were further crystallized if possible.

B: Subsequent nucleophilic displacement of C-6 chlorine atom of tryptamine derivatives.

To a solution of tryptamine (160 mg, 1 mmol) in a suitable solvent (5 mL), 4,6-dichloro-5-formamidopyrimidine (230 mg, 1.2 mmol) or 2-amino-4,6-dichloro-5-formamidopyrimidine (248 mg, 1.2 mmol) and DIPEA (348 μL, 2 mmol) were added and the reaction mixture was heated in a sealed vessel on the corresponding temperature for the specified time (Table 5). Nucleophilic reagent (Table 6) was added either neat or as a solution to the crude reaction mixture from the purine nucleobase construction and the resulting mixture was heated in a sealed vessel under microwave irradiation (with the exception of reaction with thiourea, which was heated conventionally) on the corresponding temperature for the specified time.

Completion of the reaction was determined by TLC (hexane - ethyl acetate = 1:9). Purification was performed either by crystallization (precipitation of unsoluble product from the reaction mixture) or flash chromarography on silica gel (hexane - ethyl acetate or ethyl acetate - methanol gradient).

C: Construction of 6-chloropurine nucleobase using 5-amino-4,6-dichloropyrimidine

C1: *Without a free hydroxy group:* A solution of amine (free or its salt, 1 mmol), 4,6-dichloro-5-aminopyrimidine (1.5 mmol) and DIPEA (0.7 mL) in ethanol (20 mL) was heated in a pressure vessel at 105°C for 6 days. Alternatively a solution in *n*-butanol was heated in a sealed microwave vessel at 160°C for 2-8 h. Resulting reaction intermediate was purified by chromatography on silica gel, dissolved in a mixture of triethyl ortoformate (20 mL) and conc. HCl (0.25 mL) were added, and stirred at room temperature for 3 - 5 days and evaporated. Crystallization of the crude product from water - methanol mixture (95:5) afforded product as white flakes.

C2: *With a free hydroxy group:* A solution of amine (free or its salt, 1 mmol), 4,6-dichloro-5-aminopyrimidine (1.5 mmol) and DIPEA (0.7 mL) in ethanol (20 mL) was heated in a pressure vessel at 105°C for 6 days. Alternatively a solution in *n*-butanol was heated in a sealed microwave vessel at 160°C for 2 - 8 h. Resulting reaction intermediate was purified by chromatography on silica gel, dissolved in a mixture of triethyl ortoformate (20 mL) and conc. HCl (0.25 mL) were added, and stirred at room temperature for 3 - 5 days and evaporated. This residue was dissolved in a mixture of THF and 1M hydrochloric acid (1:1, 10 mL) and stirred at RT for 4 hours. After neutralization with sodium hydrogencarbonate the product was purified by column chromatography and crystallization to afford product usually as white crystals.

D: Curtius rearrangement

To a solution of carboxylic acid (5 mmol) in dry acetone (10 mL) at 0°C was added triethylamine (6 mmol) and ethyl chloroformate (5.25 mmol). After 1 h at 0°C, a solution of sodium azide (15 mmol) in water (10 mL) was added. After 1 h at 0°C reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (4 x 50 mL). Combined organic extracts were washed with sat. $NaHCO_3$ (2 x 50 mL) and water (50 mL), dried over sodium sulfate and evaporated. Oily residue was

dissolved in dioxane or toluene (10 mL) and 2M HCl (30 mL) and heater to reflux for 5 hours, evaporated and codistilled with toluene (3 x 50 mL) to afford crude amine, which was either used without further purification, was purified on Dowex 50 (H^+) or was crystallized from ethanol-diethylether mixture.

E: Construction of thymine nucleobase

Free amine substrate (1.5 mmol) was dissolved in dioxane (20 mL), ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate (1.65 mmol) was added and the reaction mixture was heated to 100°C for 3h. Dowex 50 (H^+, 5 g) was added and reaction mixture was heated to 100°C overnight. Dowex was filtered off, volatiles were evaporated, crude product was adsorbed on silica gel and purified by flash chromatography (ethyl acetate - hexane or methanol - ethyl acetate mixture) and subsequently crystallized from suitable solvent.

F: Ammonolysis

F1: *Autoclave procedure:* A solution of 6-chloropurine derivative (1 mmol) in liquid ammonia (20 ml) was heated in autoclave at 70 °C for 12 h. Ammonia was evaporated and crude compound was adsorbed on silica and purified by chromatography on silica gel. Crystallization from water-methanol mixture afforded product as colorless or white crystals.

F2: *Microwave procedure:* A solution of 6-chloropurine or 2-amino-6-chloropurine derivative (up to 1 mmol) in ethanolic ammonia (3.5M, 5 mL) was heated in a microwave reactor at 120 °C for 20 - 40 minutes. Volatiles were evaporated and crude compound was adsorbed on silica gel and purified by flash chromatography (methanol - ethyl acetate). Crystallization from water-methanol mixture afforded pure product.

G: Nucleophilic substitution of C-6 chlorine atom of purine nucleobase with cyclopropylamine

G1: *Conventional method:* A solution of 6-chloropurine derivative (1 mmol) in cyclopropylamine (2 mL) was stirred at RT overnight. Volatiles were evaporated, crude product was adsorbed on silica and purified by column chromatography and crystallization.

G2: *Microwave procedure:* A solution of 6-chloropurine or 2-amino-6-chloropurine derivative (1 mmol) and cyclopropylamine (10 mmol) in ethanol (5 mL) was heated in a microwave reactor at 140 °C for 10 - 40 min. Volatiles were evaporated, crude product was adsorbed on silica and purified by column chromatography and crystallization. Poorly soluble products were collected on a filter and thoroughly washed with water and methanol.

H: Nucleophilic substitution of C-6 chlorine atom of purine nucleobase with dimethylamine

H1: *Conventional method:* A solution of 6-chloropurine derivative (1 mmol) in dimethylamino dimethylcarbamate (2 mL) was stirred at RT overnight. Volatiles were evaporated, crude product was adsorbed on silica and purified by column chromatography and crystallization.

H2: *Microwave procedure:* A solution of substrate (0.5 mmol) in DMF (3 mL) was subjected to microwave irradiation (sealed vessel, 200°C, 2 min). Volatiles were evaporated, crude product was adsorbed on silica and purified by column chromatography and crystallization.

I: Nucleophilic substitution of C-6 chlorine atom of purine nucleobase with thiourea

A solution of 6-chloropurine derivative (0.5 mmol) and thiourea (0.6 mmol) in dry ethanol (4 ml) was heated in a pressure vessel at 105 °C overnight. Poorly soluble product was collected on a paper filter and washed thoroughly with ethanol and diethylether.

J: Acid catalyzed hydrolysis of 2-amino-6-chloropurine substrates to guanine derivatives

A solution of 2-amino-6-chloropurine derivative (0.5 mmol) in TFA - water mixture (2:1, 6 mL) was stirred at RT overnight. Volatiles were evaporated and crude product was codistilled with ethanol (3 x 10 mL), NH_4OH (10 mL) and ethanol (2 x10 ml). Poorly soluble product was shortly boiled in water-methanol mixture (1:1), collected on a filter and thoroughly washed with water, ethanol and diethylether.

K: Alkylation of secondary hydroxyl group with diisopropyl tosylmethanphosphonate and subsequent hydrolysis

K1: To a solution of substrate (1 mmol) and (*t*-BuO)$_2$Mg (1.5 mmol) in dry DMF (25 mL) a solution of diisopropyl tosylmethanphosphonate (1.5 mmol) in DMF (5 mL) was added and the mixture was heated to 60°C for 3 days. Volatiles were evaporated, crude product was adsorbed on silica gel and purified by flash chromatography to afford phosphonate diisopropyl ester.

K2: To a solution of diisopropyl phosphonate (0.5 mmol) in dry DCM (10 mL) was added TMSBr (0.7 mL) and the reaction mixture was stirred at RT for 24h. Volatiles were evaporated and crude product was codistiled with dry ethanol (3 x 15 mL), to afford free phosphonate as a clear solid or white lyophilizate. Purification on a short C-18 column (methanol - water) is sometimes necessary for sufficient purity of the product.

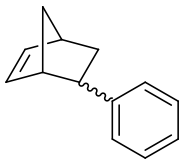
L: Preparation of phosphoramidates

To a solution of substrate (0.5 mmol) in dry THF (10 mL) was added *t*-BuMgCl (1M solution, 1 mL) and a solution of phenylmethoxyalaninyl phosphochloridate (1 mmol) in dry THF (5 mL). Reaction mixture was stirred at RT for 3 days and then quenched with sat. solution of ammonium chloride. All volatiles were evaporated and flash chromatography of the residue (methanol - ethyl acetate) afforded product as clear solid or white lyophilizate.

5.3. Diels-Alder reactions leading to variously substituted norbornene precursors

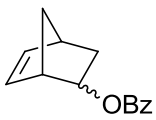
General method for the Diels-Alder reactions (Tables 1 and 2)

A 1:2 molar mixture of dicyclopentadiene **217** (1.5 mmol) and a corresponding dienophile (3 mmol) with additional 10 mg of hydroquinone or an equimolar mixture of chlorinated diene **219** or **195** (2 mmol) and a corresponding dienophile (2 mmol) with 10 mg of hydroquinone was heated in a sealed microwave reactor at specified temperature for a given period of time (Tables 1 and 2). Crude reaction mixture (sufficient conversion of diene determined by GC-MS) was chromatographed on silica gel (1-3% ethyl acetate in hexane). Chlorinated compounds with suitable melting point may also be crystallized from methanol with a few drops of water.



(1*R,4*R**,5*R**)-5-Phenylbicyclo[2.2.1]hept-2-ene (2e)**[112c]

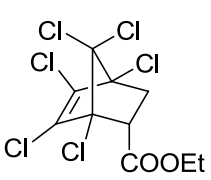
Used dienophile: styrene. Yield 410 mg (80 %) as a colorless liquid (chromatographically inseparable mixture of *endo*/*exo* isomers 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (ddd, 1H, J_{gem} = 11.8, $J_{6en,5}$ = 4.8, $J_{5en,7a}$ = 2.5, H-6endo), 1.49 (dm, 1H, J_{gem} = 8.1, H-7b), 1.53 (dm, 1H, J_{gem} = 8.1, H-7a), 2.22 (ddd, 1H, J_{gem} = 11.8, $J_{6ex,5}$ = 9.3, $J_{6ex,1}$ = 3.8, H-6exo), 2.98 (m, 1H, H-1), 3.11 (m, 1H, H-4), 3.41 (m, 1H, H-5), 5.82 (ddm, 1H, $J_{3,2}$ = 5.7, $J_{3,4}$ = 2.9, H-3), 6.28 (ddm, 1H, $J_{2,3}$= 5.7, $J_{2,1}$ = 3.1, H-2), 7.15 – 7.33 (m, 5H, H-2', H-3', H-4'). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 32.94 (C-6), 43.19 (C-1), 43.47 (C-5), 48.58 (C-4), 50.22 (C-7), 125.57 (C-4'), 127.59 (C-3'), 128.23 (C-2'), 132.79 (C-3), 137.15 (C-2), 145.02 (C-1'). HRMS (ESI) *m/z* calculated for $C_{13}H_{14}$: 170.1096, found: 170.1091.



(1*R,2*R**,4*R**)-Bicyclo[2.2.1]hept-5-en-2-yl benzoate (118g)**[112e]

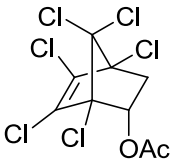
Used dienophile: vinyl benzoate. Yield 525 mg (82 %) as a colorless liquid (chromatographically separable mixture of *endo*/*exo* isomers 7:2). Characterization was performed for previously undescribed *endo* isomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (dm, 1H, J_{gem} = 12.6, H-3endo), 1.42 (dm, 1H, J_{gem} = 8.9, H-7b), 1.54 (dm, 1H, J_{gem} = 8.9, H-7a), 2.26 (ddd, 1H, J_{gem} = 12.6, $J_{3ex,2}$ = 8.1, $J_{3ex,4}$ = 3.7, H-3exo), 2.92 (m, 1H, H-4), 3.27 (m, 1H, H-1), 5.54 (ddd, 1H, $J_{2,3ex}$ = 8.1, $J_{2,1}$ = 4.0, $J_{2,3en}$ = 2.6, H-2), 6.08 (ddm, 1H, $J_{6,5}$ = 5.7, $J_{6,1}$ = 2.9, H-6), 6.39 (ddm, 1H, $J_{5,6}$ = 5.7, $J_{5,4}$ = 3.1, H-5), 7.42 (m, 2H, H-3'), 7.54 (m, 1H, H-4'), 7.97 (m, 2H,

H-2'). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 34.83 (C-3), 42.30 (C-4), 45.96 (C-1), 47.66 (C-7), 75.62 (C-2), 128.28 (C-3'), 129.47 (C-2'), 130.54 (C-1'), 131.58 (C-6), 132.73 (C-4'), 138.59 (C-5), 166.71 (COO). HRMS (ESI) *m/z* calculated for $C_{14}H_{14}O_2$: 214.0994, found: 214.0988.



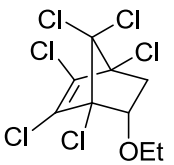
Ethyl (1*R,2*S**,4*S**)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene-2-carboxylate (220a)**[113a]

Used dienophile: ethyl acrylate. Yield 603 mg (81 %) as a white solid or 519 (71%) as white crystals (m. p. = 70°C, lit = 69°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, 3H, $J_{CH3,CH2}$ = 7.1,CH_3), 2.58 (dd, 1H, J_{gem} = 12.5, $J_{3en,2}$ = 4.1, H-3endo), 2.68 (dd, 1H, J_{gem} = 12.5, $J_{3ex,2}$ = 8.9, H-3exo), 3.61 (dd, 1H, $J_{2,3ex}$ = 8.9, $J_{2,3en}$ = 4.1, H-2), 4.14 - 4.27 (m, 2H, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.06 (CH_3), 38.10 (C-3), 50.49 (C-2), 62.26 (CH_2), 78.44 and 80.84 (C-1, C-4), 102.53 (C-7), 129.53 (C-6), 132.32 (C-5), 168.41 (COO). HRMS (ESI) *m/z* calculated for $C_{10}H_8O_2Cl_6$: 369.8655, found: 369.8664.



(1*R,2*R**,4*S**)-1,4,5,6,7,7-Hexachlorobicyclo[2.2.1]hept-5-en-2-yl acetate (220b)**[113b]

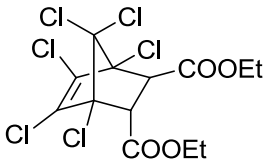
Used dienophile: vinyl acetate. Yield 580 mg (81 %) after chromatography as a colorless solid (m. p. = 44°C, lit = 44°C) or 21.3 g (81 %, starting from 73 mmol of **219**) after distillation under reduced pressure (0.04 mbar, 110 - 120°C) as a yellowish oil which solidifies on standing. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01 (dd, 1H, J_{gem} = 13.3, $J_{3en,2}$ = 2.5, H-3endo), 2.11 (s, 3H, CH_3), 3.05 (dd, 1H, J_{gem} = 13.3, $J_{3ex,2}$ = 7.7, H-3exo), 5.70 (dd, 1H, $J_{2,3ex}$ = 7.7, $J_{2,3en}$ = 2.5, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.51 (CH_3), 43.42 (C-3), 77.03 (C-2), 78.21 and 81.27 (C-1, C-4), 100.78 (C-7), 130.22 (C-6), 132.58 (C-5), 169.63 (COO). HRMS (ESI) *m/z* calculated for $C_9H_6O_2Cl_6$: 355.8499, found: 355.8500.



Ethyl (1*R,2*R**,4*S**)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-en-2-yl ether (220c)**[113c]

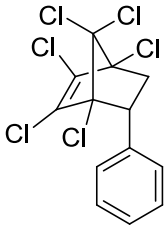
Used dienophile: ethylvinyl ether. Yield 215 mg (31 %) as a brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (t, 3H, $J_{CH3,CH2}$ = 7.0, CH_3), 1.98 (dd, 1H, J_{gem} = 12.8, $J_{3en,2}$ = 2.3, H-3endo), 2.87 (dd, 1H, J_{gem} = 12.8, $J_{3ex,2}$ = 7.5, H-3exo),

3.62 and 3.85 (dq, 2H, J_{gem} = 9.3, $J_{CH2,CH3}$ = 7.0, OCH_2), 4.47 (dd, 1H, $J_{2,3ex}$ = 7.5, $J_{2,3en}$ = 2.3, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.25 (CH_3), 43.71 (C-3), 67.38 (OCH_2), 78.28 and 82.88 (C-1, C-4), 83.71 (C-2), 101.30 (C-7), 130.34 (C-6), 131.47 (C-5). HRMS (ESI) *m/z* calculated for $C_9H_8OCl_6$: 341.8706, found: 341.8710.



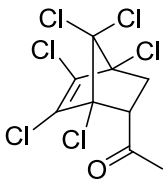
Diethyl (1*R,2*S**,3*S**,4*S**)-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hept-5-ene-2,3-dicarboxylate (220d)**[113b]

Used dienophile: diethyl fumarate. Yield 320 mg (36 %) as a brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 and 1.34 (t, 6H, $J_{CH3,CH2}$ = 7.2, CH_3), 3.50 (d, 1H, $J_{3,2}$ = 5.4, H-3), 4.24 (d, 1H, $J_{2,3}$ = 5.4, H-2), 4.18 - 4.34 (m, 4H, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.07 (CH_3), 51.72 (C-3), 53.24 (C-2), 62.41 and 62.66 (CH_2), 79.89 and 79.99 (C-1, C-4), 101.94 (C-7), 131.85 (C-6), 133.75 (C-5), 166.07 and 168.07 (COO). HRMS (ESI) *m/z* calculated for $C_{13}H_{12}O_4Cl_6$: 441.8867, found: 441.8881.



(1*R,4*S**,5*R**)-1,2,3,4,7,7-Hexachloro-5-phenylbicyclo[2.2.1]hept-2-ene (220e)**[113d]

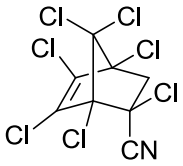
Used dienophile: styrene. Yield 720 mg (95 %) as a white solid or 636 mg (84%) as white crystals (m. p. = 69-70°C, lit = 73°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (dd, 1H, J_{gem} = 13.0, $J_{6en,5}$ = 4.2, H-6endo), 2.93 (dd, 1H, J_{gem} = 13.0, $J_{6ex,5}$ = 9.2, H-6exo), 3.99 (dd, 1H, $J_{5,6ex}$ = 9.1, $J_{5,6en}$ = 4.2, H-5), 7.11 (m, 2H, H-2'), 7.32 – 7.36 (m, 3H, H-3', H-4'). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 40.73 (C-6), 51.66 (C-5), 78.98 and 84.11 (C-1, C-4), 102.85 (C-7), 128.44 (C-4'), 128.53 (C-3'), 128.93 (C-2'), 131.05 and 131.17 (C-2, C-3), 134.22 (C-1'). HRMS (ESI) *m/z* calculated for $C_{13}H_8Cl_6$: 373.8757, found: 373.8765.



1-[(1*R,2*S**,4*S**)-1,4,5,6,7,7-Hexachlorobicyclo[2.2.1]hept-5-en-2-yl]ethanone (220f)**[113e]

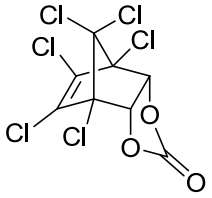
Used dienophile: methyl vinyl ketone. Yield 571 mg (84 %) as a white solid or 480 mg (70%) as white crystals (m. p. = 73°C, lit = 74°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.46 (dd, 1H, J_{gem} = 12.4, $J_{3ex,2}$ = 8.6, H-3exo), 2.69 (dd, 1H, J_{gem} = 12.4, $J_{3en,2}$ = 4.0, H-3endo), 3.74 (dd, 1H, $J_{2,3ex}$ = 8.6, $J_{2,3en}$ = 4.0, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 31.39 (CH_3), 36.45

(C-3), 57.13 (C-2), 78.42 and 81.01 (C-1, C-4), 102.77 (C-7), 128.29 (C-6), 132.36 (C-5), 201.76 (CO). HRMS (ESI) *m/z* calculated for $C_9H_6OCl_6$: 339.8550, found: 339.8555.



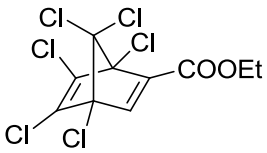
(1*R,4*S**)-1,2,4,5,6,7,7-Heptachlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile (220h)**[113f]

Used dienophile: 2-chloroacrylonitrile. Yield 475 mg (66 %) as a white solid or 380 mg (52%) as white crystals (m. p. = 167-168°C, lit = 178-180°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.80 and 3.54 (d, 2H, J_{gem} = 14.1, H-3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 49.86 (C-3), 61.62 (C-2), 77.20 and 85.00 (C-1, C-4), 99.86 (C-7), 114.42 (CN), 132.41 (C-6), 134.22 (C-5). HRMS (ESI) *m/z* calculated for $C_8H_2NCl_7$: 356.8007, found: 356.8011.



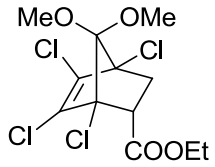
(1*R,2*R**,6*S**,7*S**)-1,7,8,9,10,10-Hexachloro-3,5-dioxatricyclo [5.2.1.0^{2,6}]dec-8-en-4-one (220i)**[113g]

Used dienophile: vinylene carbonate. Yield 480 mg (77 %) as a white solid or 450 (63%) as white crystals (m. p. = 235°C, lit = 233°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.38 (s, 2H, H-2, H-6). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 80.63 (C-1, C-7), 82.55 (C-2, C-6), 98.44 (C-10), 131.52 (C-8, C-9), 151.38 (C-4). HRMS (ESI) *m/z* calculated for $C_8H_2O_3Cl_6$: 355.8135, found: 355.8143.



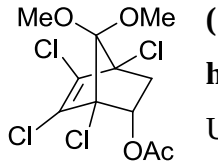
Ethyl (1*R,4*S**)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (220j)**[113h]

Used dienophile: ethyl propiolate. Yield 512 mg (69 %) as a clear oil, which slowly decomposes (completely cca 1 month) at room temperature. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (t, 3H, $J_{CH3,CH2}$ = 7.2, CH_3), 4.24 - 4.34 (m, 2H, CH_2), 7.37 (s, 1H, H-3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.08 (CH_3), 61.98 (CH2), 82.59 and 83.17 (C-1, C-4), 115.51 (C-7), 137.47 (C-6), 138.30 (C-5), 142.75 (C-2), 148.44 (C-3), 160.08 (COO). HRMS (ESI) *m/z* calculated for $C_{10}H_6O_2Cl_6Na$: 390.83912, found: 390.84009.



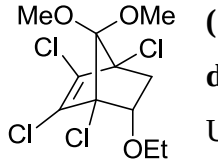
Ethyl (1*R,2*R**,4*S**)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo [2.2.1]hept-5-ene-2-carboxylate (221a)**[113i]

Used dienophile: ethyl acrylate. Yield 582 mg (80 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (t, 3H, $J_{CH3,CH2}$ = 7.1, CH_3), 2.27 (dd, 1H, J_{gem} = 11.7, $J_{3en,2}$ = 4.2, H-3endo), 2.51 (dd, 1H, J_{gem} = 11.7 $J_{3ex,2}$ = 9.2, H-3exo), 3.42 (dd, 1H, $J_{2,3ex}$ = 9.2, $J_{2,3en}$ = 4.2, H-2), 3.56 and 3.62 (s, 6H, OMe), 4.12 and 4.20 (dq, 4H, J_{gem} = 10.8, $J_{CH2,CH3}$ = 7.2, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.08 (CH_3), 38.90 (C-3), 50.48 (C-2), 51.71 and 51.78 (OMe), 61.65 (CH_2), 74.12 and 76.92 (C-1, C-4), 111.95 (C-7), 127.99 (C-6), 130.43 (C-5), 169.70 (COO). HRMS (ESI) *m/z* calculated for $C_{12}H_{14}O_4Cl_4$: 361.9646, found: 361.9645.



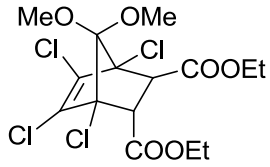
(1*R,2*S**,4*S**)-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1] hept-5-en-2-yl acetate (221b)**[113j]

Used dienophile: vinyl acetate. Yield 528 mg (75 %) as a white solid or 460 mg (66%) as white crystals (m. p. = 81°C, lit = 84°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (dd, 1H, J_{gem} = 12.7, $J_{3en,2}$ = 2.5, H-3endo), 2.06 (s, 3H, CH_3), 2.81 (dd, 1H, J_{gem} = 12.7, $J_{3ex,2}$ = 7.8, H-3exo), 3.56 and 3.60 (s, 6H, OMe), 5.49 (dd, 1H, $J_{2,3ex}$ = 7.8, $J_{2,3en}$ = 2.5, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.65 (CH_3), 43.76 (C-3), 51.72 and 52.64 (OMe), 73.87 and 77.26 (C-1, C-4), 77.76 (C-2), 111.75 (C-7), 127.80 (C-6), 130.97 (C-5), 170.19 (CO). HRMS (ESI) *m/z* calculated for $C_{11}H_{12}O_4Cl_4$: 347.9490, found: 347.9498.



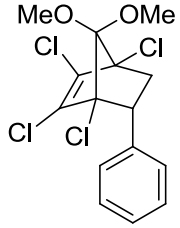
(1*R,4*S**,5*R**)-1,2,3,4-Tetrachloro-5-ethoxy-7,7-dimethoxybicyclo[2.2.1]hept-2-ene (221c)**[113k]

Used dienophile: ethylvinyl ether. Yield 533 mg (79 %) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (t, 3H, $J_{CH3,CH2}$ = 7.0, CH_3), 1.74 (dd, 1H, J_{gem} = 12.0, $J_{3en,2}$ = 2.3, H-3endo), 2.62 (dd, 1H, J_{gem} = 12.0, $J_{3ex,2}$ = 7.6, H-3exo), 3.56 and 3.59 (s, 6H, OCH_3), 3.56 and 3.75 (m, 2H, OCH_2), 4.29 (dd, 1H, $J_{2,3ex}$ = 7.7, $J_{2,3en}$ = 2.3, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.31 (CH_3), 43.87 (C-3), 51.54 and 52.59 (OMe), 66.68 (OCH2), 74.14 and 79.03 (C-1, C-4), 83.76 (C-2), 111.76 (C-7), 127.97 (C-6), 129.90 (C-5). HRMS (ESI) *m/z* calculated for $C_{11}H_{14}O_3Cl_4$: 333.9697, found: 333.9707.



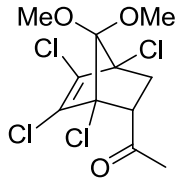
Diethyl (1*R,2*S**,3*S**,4*S**)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (221d)**

Used dienophile: diethyl fumarate. Yield 628 mg (72 %) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 and 1.32 (t, 6H, $J_{CH3,CH2}$ = 7.2 CH_3), 3.19 (d, 1H, $J_{3en,2}$ = 5.3, H-3), 3.55 and 3.57 (s, 6H, OMe), 4.03 (d, 1H, $J_{2,3}$ = 5.4, H-2), 4.12 - 4.29 (m, 4H, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.08 and 14.19 (CH_3), 51.69 and 52.26 and 52.60 and 53.41 (C-2, C-3, OMe), 61.76 and 61.99 (CH_2), 75.79 and 75.80 (C-1, C-4), 111.72 (C-7), 129.91 (C-6), 131.41 (C-5), 167.14 and 169.11 (COO). HRMS (ESI) *m/z* calculated for $C_{15}H_{19}O_6Cl_4$: 434.99303, found: 434.99300.



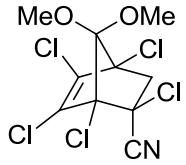
(1*R,4*S**,5*S**)-1,2,3,4-Tetrachloro-7,7-dimethoxy-5-phenylbicyclo[2.2.1] hept-2-ene (221e)**[113l]

Used dienophile: styrene. Yield 685 mg (93 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25 (dd, 1H, J_{gem} = 12.3, $J_{6en,5}$ = 4.4, H-6endo), 2.77 (dd, 1H, J_{gem} = 12.3, $J_{6ex,5}$ = 9.4, H-6exo), 3.58 and 3.69 (s, 6H, OMe), 3.79 (dd, 1H, $J_{5,6ex}$ = 9.4, $J_{5,6en}$ = 4.4, H-5), 7.07 (m, 2H, H-2'), 7.28 – 7.33 (m, 3H, H-3', H-4'). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 41.84 (C-6), 51.70 (C-5 and OMe), 52.67 (OMe), 74.80 and 80.21 (C-1, C-4), 112.29 (C-7), 127.81 (C-4'), 128.19 (C-3'), 129.08 (C-2'), 129.08 (C-3), 129.62 (C-2), 135.84 (C-1'). HRMS (ESI) *m/z* calculated for $C_{15}H_{14}O_2Cl_4Na$: 388.96401, found: 388.96330.



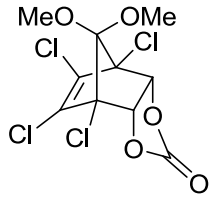
1-[(1*R,2*R**,4*S**)-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo [2.2.1]hept-5-en-2-yl]ethanone (221f)**[113l]

Used dienophile: methyl vinyl ketone. Yield 500 mg (75 %) as a white solid or 460 mg (69%) as white crystals (m. p. = 86°C, lit = 85-87°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (dd, 1H, J_{gem} = 11.7, $J_{3ex,2}$ = 8.8, H-3exo), 2.34 (s, 3H, CH_3), 2.40 (dd, 1H, J_{gem} = 11.7, $J_{3en,2}$ = 4.2, H-3endo), 3.59 (dd, 1H, $J_{2,3ex}$ = 8.8, $J_{2,3en}$ = 4.2, H-2), 3.56 and 3.64 (s, 6H, OMe). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 31.69 (CH_3), 37.10 (C-3), 51.76 and 52.80 (OMe), 57.12 (C-2), 74.11 and 77.18 (C-1, C-4), 112.18 (C-7), 126.76 (C-6), 130.62 (C-5), 203.80 (CO). HRMS (ESI) *m/z* calculated for $C_{11}H_{12}O_3Cl_4Na$: 354.94328, found: 354.94328.



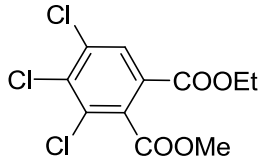
(1*R,4*R**)-1,2,4,5,6-Pentachloro-7,7-dimethoxybicyclo[2.2.1] hept-5-ene-2-carbonitrile (221h)**[113f]

Used dienophile: 2-chloroacrylonitrile. Yield 480 mg (69 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (d, 1H, J_{gem} = 13.4, H-3endo), 3.36 (d, 1H, J_{gem} = 13.4, H-3exo), 3.61 and 3.71 (s, 6H, OMe). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 51.21 (C-3), 51.97 and 53.06 (OMe), 61.84 (C-2), 72.50 and 81.50 (C-1, C-4), 111.62 (C-7), 116.02 (CN), 128.78 (C-6), 133.32 (C-5). HRMS (ESI) *m/z* calculated for $C_{10}H_8NO_2Cl_5$: 348.8998, found: 348.8983.



(1*R,2*S**,6*R**,7*S**)-1,7,8,9-Tetrachloro-10,10-dimethoxy-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-4-one (221i)**[113g]

Used dienophile: vinylene carbonate. Yield 530 mg (76 %) as a white solid or 507 mg (73%) as white crystals (m. p. = 158-159°C, lit = 157-158°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60 and 3.62 (s, 6H, OMe), 5.16 (s, 2H, H-2, H-6). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 52.34 and 52.97 (OMe), 76.54 (C-1, C-7), 83.06 (C-2, C-6), 112.16 (C-10), 128.92 (C-8, C-9), 152.25 (C-4). HRMS (ESI) *m/z* calculated for $C_{10}H_8O_5Cl_4Na$: 370.90181, found: 370.90209.

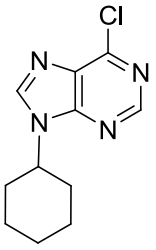


Ethyl methyl 4,5,6-trichlorobenzene-1,3-dicarboxylate (222)

Used dienophile: ethyl propiolate. Yield 510 mg (70 %) as an off-white solid (m. p. = 50°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (t, 3H, $J_{CH3,CH2}$ = 7.2, $CH_2\mathbf{CH_3}$), 3.98 (s, 3H, OMe), 4.37 (q, 2H, $J_{CH2,CH3}$ = 7.2, CH_2), 8.06 (s, 1H, H-1). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.05 (CH_2-$\mathbf{CH_3}$), 53.18 (OMe), 62.51 (CH_2), 127.41 and 132.10 and 134.94 and 135.04 and 136.87 (C-1, C-3, C-4, C-5, C-6), 129.87 (C-2), 162.84 (**COO**Et), 165.71 (**COO**Me). HRMS (ESI) *m/z* calculated for $C_{11}H_9O_4Cl_3$: 309.9566, found: 309.9565.

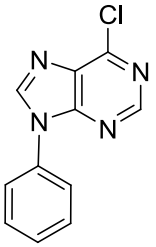
5.4. Construction of variously substituted purine nucleobases on amine substrates

Following compounds (Tables 5 and 6) were prepared according to the general method A (**225** - **256**) or B (**257** - **268**). Chromatography mobile phase, crystallization solvent system and analytical data (new compounds) are assigned to each compound.



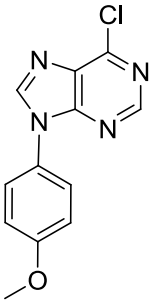
6-Chloro-9-cyclohexyl-9*H*-purin (225)

Best achieved **y**ield 203 mg (86 %). Mobile phase: 25-35% ethyl acetate in hexane. Crystallization from cyclohexane (slighly orange crystals). Spectral characteristics match those described in literature.[123a]



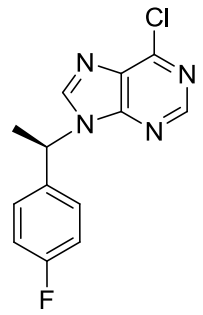
6-Chloro-9-phenyl-9*H*-purin (227)

Best achieved **y**ield 185 mg (80 %). Mobile phase: 30-40% ethyl acetate in hexane. Crystallization from cyclohexane (white crystals). Spectral characteristics match those described in literature.[123b]



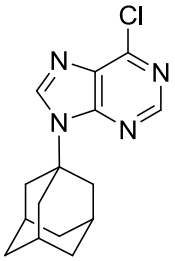
6-Chloro-9-(4-methoxyphenyl)-9*H*-purine (228)

Best achieved **y**ield 234 mg (90 %). Mobile phase: 50-70% ethyl acetate in hexane. Crystallization from toluene (white crystals), m.p. 202 - 203 °C (decomp.). ^{1}H NMR (500 MHz, DMSO): δ 3.84 (s, 3H, CH_3), 7.18 (m, 2H, H-3'), 7.76 (m, 2H, H-2'), 8.81 (s, 1H, H-2), 9.00 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 55.77 (CH_3), 114.91 (C-3'), 125.67 (C-2'), 126.99 (C-1'), 131.41 (C-5), 146.78 (C-8), 149.62 (C-6), 151.81 (C-4), 152.22 (C-2), 159.36 (C-4'). ESI MS *m/z* (%): 276.3 (100) [M+H], 298.3 (77) [M+Na]. HRMS ESI ($C_{12}H_{11}ON_5Cl$) calculated: 276.06466; found: 276.06483. For $C_{12}H_9N_4OCl$ (260.68) calculated: 55.29% C, 3.48% H, 21.49% N, 13.60% Cl; found: 55.48% C, 3.49% H, 21.30% N, 13.56% Cl.



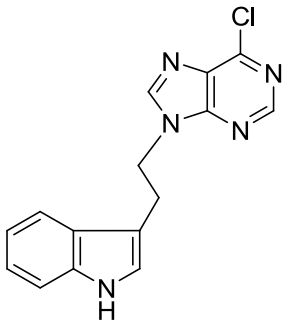
6-Chloro-9-[(1*R*)-1-(4-fluorophenyl)ethyl]-9*H*-purine (229)

Best achieved **y**ield 260 mg (94 %). Mobile phase: 30-50% ethyl acetate in hexane (pale yellow oil). ^{1}H NMR (500 MHz, DMSO): δ 2.00 (d, 3H, J_{CH3-CH} = 7.2, CH_3), 6.00 (q, 1H, J_{CH-CH3} = 7.2, **CH**-CH_3), 7.18 (m, 2H, H-3'), 7.47 (m, 2H, H-2'), 8.76 (s, 1H, H-2), 8.97 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 20.42 (CH_3), 54.00 (**CH**-CH_3), 115.69 (d, $J_{3',F}$ = 21.5, C-3'), 128.77 (d, $J_{2',F}$ = 8.4, C-2'), 131.29 (C-5), 136.99 (d, $J_{1',F}$ = 3.1, C-1'), 146.07 (C-8), 149.35 (C-6), 151.65 (C-2 and C-4), 161.81 (d, $J_{4',F}$ = 244.3, C-4'). ESI MS *m/z* (%): 277.0 (7) [M+H], 299.0 (100) [M+Na]; HRMS ESI ($C_{13}H_{11}N_4ClF$) calculated: 277.08508; found: 277.08514. For $C_{13}H_{10}N_4FCl$ (276.70) calculated: 56.43% C, 3.64% H, 20.25% N, 6.87% F, 12.81% Cl; found: 56.59% C, 3.72% H, 20.40% N, 6.55% F, 12.69% Cl.



6-Chloro-9-(1-adamantyl)-9*H*-purine (230)

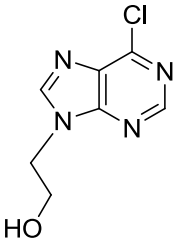
Best achieved **y**ield 162 mg (56 %). Mobile phase: 20-35% ethyl acetate in hexane. Crystallization from toluene - cyclohexane mixture (slighly orange crystals). Spectral characteristics match those described in literature.[123c]



6-Chloro-9-[2-(1*H*-indol-3-yl)ethyl]-9*H*-purin (231)

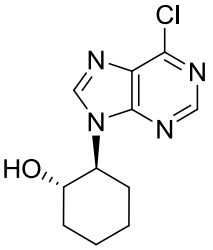
Best achieved **y**ield 277 mg (93 %). Mobile phase: 40-60% ethyl acetate in hexane. Crystallization from cyclohexane (white crystals), m.p. 187 - 189 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.31 (m, 2H, 3'-CH_2), 4.58 (m, 2H, N-CH_2), 6.96 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.04 - 7.08 (m, 2H, H-2', H-6'), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.50 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 8.54 (s, 1H, H-8), 8.79 (s, 1H, H-2), 10.86 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 25.24 (3'-CH_2), 44.74 (N-CH_2), 110.03 (C-3'), 111.63 (C-7'), 118.18 (C-4'), 118.58 (C-5'), 121.26 (C-6'), 123.43 (C-2'), 127.01 (C-3'a), 130.97 (C-5), 136.35 (C-7'a), 147.64 (C-8), 149.05 (C-6), 151.58 (C-2), 152.10 (C-4). ESI MS *m/z* (%): 298.1 (32) [M+H], 320.1 (100) [M+Na]; HRMS ESI

($C_{15}H_{13}N_5Cl$) calculated: 298.08540; found: 298.08540. For $C_{15}H_{12}N_5Cl$ (297.74) calculated: 60.51% C, 4.06% H, 23.52% N, 11.91% Cl; found: 60.50% C, 4.01% H, 23.68% N, 11.87% Cl.



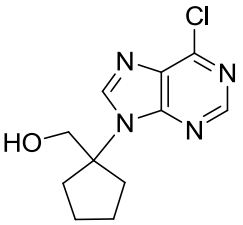
2-(6-Chloro-9*H*-purin-9-yl)ethanol (232)

Best achieved **y**ield 187 mg (94 %). Mobile phase: 70-90% ethyl acetate in hexane. Crystallization from toluene (white crystals), m.p. 159 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.79 (q, 2H, $J_{2',OH} = J_{2',1'} = 5.4$, H-2'), 4.35 (t, 2H, $J_{1',2'} = 5.4$, H-1'), 5.01 (t, 1H, $J_{OH,2'} = 5.6$, OH), 8.65 (s, 1H, H-8), 8.77 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): δ 46.77 (C-1'), 59.04 (C-2'), 131.03 (C-5), 148.15 (C-8), 148.97 (C-6), 151.51 (C-2), 152.28 (C-4). ESI MS *m/z* (%): 199.1 (79) [M+H], 221.1 (100) [M+Na]; HRMS ESI ($C_7H_8ON_4Cl$) calculated: 199.03812; found: 199.03809. For $C_7H_7N_4OCl$ (198.61) calculated: 42.33% C, 3.55% H, 28.21% N, 17.85% Cl; found: 42.51% C, 3.69% H, 28.33% N, 17.82% Cl.



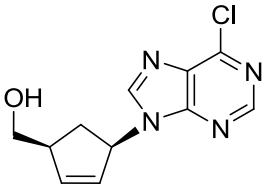
(1*R,2*R**)-2-(6-Chloro-9*H*-purin-9-yl)cyclohexanol (233)**

Best achieved **y**ield 215 mg (85 %). Mobile phase: 70-90% ethyl acetate in hexane. Crystallization from toluene - cyclohexane mixture (white crystals), m.p. 238 - 239 °C. ^{1}H NMR (500 MHz, DMSO): δ 1.31 - 1.42 (m, 3H, H-4ax, H-5ax, H-6ax), 1.74 - 1.79 (m, 2H, H-4eq, H-5eq), 1.95 - 2.04 (m, 2H, H-3eq, H-6eq), 2.14 (m, 1H, H-3ax), 4.01 (m, 1H, H-1), 4.26 (ddd, 1H, $J_{2,3ax} = 12.5$, $J_{2,1} = 10.0$, $J_{2,3eq} = 4.3$, H-2), 4.94 (d, 1H, $J_{OH,1} = 5.3$, OH), 8.74 and 8.75 (s, 2H, H-2', H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.13 and 24.85 (C-4, C-5), 30.78 (C-3), 34.85 (C-6), 62.14 (C-2), 70.28 (C-1), 131.39 (C-5'), 147.14 (C-8'), 148.97 (C-6'), 151.18 (C-2'), 152.36 (C-4'). ESI MS *m/z* (%): 253.1 (22) [M+H], 275.1 (100) [M+Na]; HRMS ESI ($C_{11}H_{13}ON_4ClNa$) calculated: 275.06701; found: 275.06708. For $C_{11}H_{13}N_4ClO$ (252.70) calculated: 52.28% C, 5.19% H, 22.17% N, 14.03% Cl; found: 52.33% C, 5.22% H, 22.40% N, 13.89% Cl.



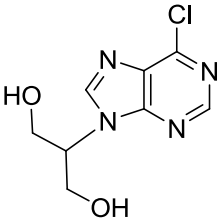
(1-(6-Chloro-9*H*-purin-9-yl)cyclopentyl)methanol (234)

Best achieved **y**ield 154 mg (61 %). Mobile phase: 1-2% methanol in ethyl acetate. Crystallization from hexane - ethyl acetate mixture (white crystals), m.p. 177.5 °C. ^{1}H NMR (500 MHz, DMSO): δ 1.69 - 1.74 (m, 4H, H-3'), 2.27 and 2.39 (m, 2H, H-2'), 3.71 (d, 2H, $J_{CH2,OH}$ = 5.9, CH_2O), 5.01 (t, 1H, $J_{OH,CH2}$ = 5.9, OH), 8.64 (s, 1H, H-8), 8.74 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): δ 22.70 (C-3'), 33.55 (C-2'), 64.15 (CH_2O), 71.99 (C-1'), 132.01 (C-5), 147.49 (C-8), 149.11 (C-6), 150.77 (C-2), 152.32 (C-4). ESI MS *m/z* (%): 253.1 (5) [M+H], 275.1 (100) [M+Na]; HRMS ESI ($C_{11}H_{14}ON_4Cl$) calculated: 253.08507; found: 253.08507. For $C_{11}H_{13}N_4ClO$ (252.70) calculated: 52.28% C, 5.19% H, 22.17% N, 14.03% Cl; found: 52.30% C, 5.23% H, 22.05% N, 14.20% Cl.



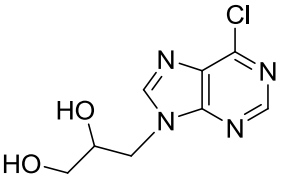
((1*S*,4*R*)-4-(-6-Chloro-9*H*-purin-9-yl)cyclopent-2-enyl)methanol (235)

Best achieved **y**ield 175 mg (70 %). Mobile phase: 1-2% methanol in ethyl acetate. Crystallization from toluene - ethyl acetate mixture. Spectral characteristics match those described in literature.[123d]



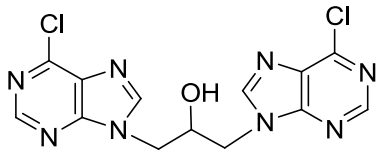
2-(6-Chloro-9*H*-purin-9-yl)propan-1,3-diol (236)

Best achieved **y**ield 206 mg (90 %). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from ethyl acetate (brownish crystals), m.p. 186.5 - 187 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.84 (ddd, 2H, J_{gem} = 11.6, $J_{2'b,OH}$ = 5.6, $J_{2'b,1'}$ = 4.9, H-2'b), 3.93 (ddd, 2H, J_{gem} = 11.6, $J_{2'a,1'}$ = 7.5, $J_{2'b,OH}$ = 5.6, H-2'a), 4.69 (m, 1H, H-1'), 5.06 (t, 2H, $J_{OH,2'}$ = 5.6, OH), 8.70 (s, 1H, H-8), 8.76 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): δ 59.82 (C-2'), 60.57 (C-1'), 131.20 (C-5), 147.24 (C-8), 149.02 (C-6), 151.41 (C-2), 152.67 (C-4). ESI MS *m/z* (%): 229.1 (50) [M+H], 251.1 (100) [M+Na]; HRMS ESI ($C_8H_{10}O_2N_4Cl$) calculated: 229.04868; found: 229.04862. For $C_8H_9N_4O_2Cl$ (228.64) calculated: 42.03% C, 3.97% H, 24.50% N, 15.51% Cl; found: 42.17% C, 4.03% H, 24.24% N, 15.42% Cl.



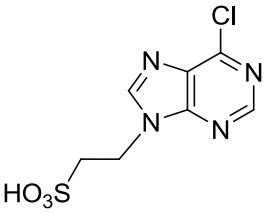
3-(6-Chloro-9*H*-purin-9-yl)propan-1,2-diol (237)

Best achieved **y**ield 151 mg (66 %). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from a small amount of ethyl acetate (brownish crystals). Spectral characteristics match those described in literature.[123e]



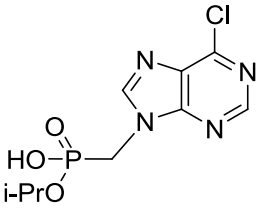
1,3-Bis(6-chloro-9*H*-purin-9-yl)propan-2-ol (238)

Best achieved **y**ield 321 mg (88 %). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from ethyl acetate (white crystals), m.p. 246-247 °C (decomp.). ^{1}H NMR (600 MHz, DMSO): δ 4.30 (dd, 2H, J_{gem} = 14.1, $J_{1'b,2'}$ = 7.9, H-1'b), 4.43 (m, 1H, H-2'), 4.52 (dd, 2H, J_{gem} = 14.1, $J_{1'a,2'}$ = 3.7, H-1'a), 5.65 (d, 1H, $J_{OH,2'}$ = 5.6, OH), 8.63 (s, 2H, H-8), 8.78 (s, 2H, H-2). ^{13}C NMR (150 MHz, DMSO): δ 47.52 (C-1'), 66.82 (C-2'), 130.94 (C-5), 148.29 (C-8), 149.06 (C-6), 151.62 (C-2), 152.40 (C-4). ESI MS *m/z* (%): 365.0 (11) [M+H], 387.0 (100) [M+Na]; HRMS ESI ($C_{13}H_{11}ON_8Cl_2$) calculated: 365.04274; found: 365.04273. For $C_{13}H_{10}N_8Cl_2O$ (365.18) calculated: 42.76% C, 2.76% H, 30.68% N, 19.42% Cl; found: 42.64% C, 2.73% H, 30.89% N, 19.55% Cl.



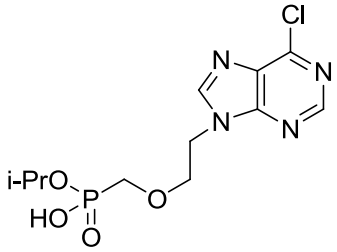
2-(6-Chloro-9*H*-purin-9-yl)ethanesulfonic acid, TEA salt (239)

Best achieved **y**ield 316 mg (87 %). Purification on HPLC (50 mM TEAB - methanol). Pale orange foam (methanol). ^{1}H NMR (500 MHz, DMSO): δ 1.17 (t, 9H, $J_{CH3,CH2}$ = 7.3, CH_3), 3.03 (m, 2H, H-2'), 3.09 (q, 6H, $J_{CH2,CH3}$ = 7.3, $\mathbf{CH_2}CH_3$), 4.54 (m, 2H, H-1'), 8.67 (s, 1H, H-8), 8.76 (s, 1H, H-2), 8.99 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 8.79 (CH_3); 41.22 (C-1'); 45.90 ($\mathbf{CH_2}CH_3$); 49.84 (C-2'); 131.00 (C-5); 148.35 (C-8); 148.78 (C-6); 151.39 (C-2); 152.09 (C-4). negESI MS *m/z* (%): 261.0 (100) [M-H]; 522.6 (8) [2M-H]; HRMS ESI ($C_7H_6O_3N_4ClS$) calculated: 260.98546; found: 260.98652. For $C_{13}H_{22}N_5ClSO_3$ (363.86) calculated: 42.91% C, 6.09% H, 19.25% N, 9.74% Cl, 8.81% S; found: 42.80% C, 6.23% H, 19.17% N, 9.67% Cl, 8.96% S.



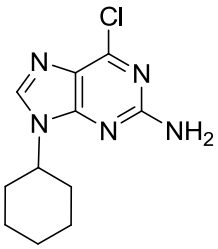
Isopropyl (6-chloro-9*H*-purin-9-yl)methylphosphonate, DIPEA salt (240)

Best achieved **y**ield 335 mg (80 %). Purification on HPLC (water - methanol). Yellow oil. ^{1}H NMR (500 MHz, DMSO): δ 0.98 (d, 6H, $J_{CH3,CH}$ = 6.2, P-O-CH-**C**$\mathbf{H_3}$), 1.20 - 1.24 (m, 15H, N-CH-**C**$\mathbf{H_3}$, N-CH_2-**C**$\mathbf{H_3}$), 3.05 (m, 2H, N-**C**$\mathbf{H_2}$-CH_3), 3.52 (m, 2H, N-**C**$\mathbf{H}$-CH_3), 4.18 - 4.26 (m, 3H, P-CH_2, P-O-**C**$\mathbf{H}$-CH_3), 8.67 (s, 1H, H-8), 8.76 (s, 1H, H-2), 9.61 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 12.37 (N-CH_2-**C**$\mathbf{H_3}$); 16.81 and 18.10 (N-CH-**C**$\mathbf{H_3}$); 24.42 (d, $J_{C-C-O-P}$ = 3.6, P-O-CH-**C**$\mathbf{H_3}$); 41.50 (d, $J_{C,P}$ = 137.8, CH_2P); 41.65 (N-**C**$\mathbf{H_2}$-CH_3); 53.29 (N-**C**$\mathbf{H}$-CH_3); 67.09 (d, J_{C-O-P} = 5.8, CH_2P); 130.39 (C-5); 147.91 (C-8); 148.84 (C-6); 151.46 (C-2); 152.17 (C-4). NegESI MS *m/z* (%): 289.0 (100) [M-H]; HRMS negESI ($C_9H_{11}O_3N_4ClP$) calculated: 289.02628; found: 289.02611.



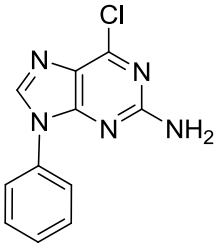
Isopropyl hydrogen (2-(6-chloro-9*H*-purin-9-yl)ethoxy)ethylphosphonate, TEA salt (241)

Best achieved **y**ield 248 mg (57 %). Purification performed on HPLC (50 mM TEAB - methanol). White foam (methanol). ^{1}H NMR (500 MHz, DMSO): δ 0.97 (d, 6H, $J_{CH3,CH}$ = 6.2, CH_3*i*Pr), 1.14 (t, 9H, $J_{CH3,CH2}$ = 7.3, N-CH_2-**C**$\mathbf{H_3}$), 2.95 (q, 6H, $J_{CH2,CH3}$ = 7.3, N-**C**$\mathbf{H_2}$-CH_3), 3.45 (d, 2H, $J_{H,C,P}$ = 8.3, P-**C**$\mathbf{H_2}$), 3.91 (m, 2H, H-2'), 4.17 (dsept, 1H, $J_{H,C,O,P}$ = 8.2, $J_{CH,CH3}$ = 6.2, CH*i*Pr), 4.47 (m, 2H, H-1'), 8.77 (s, 1H, H-2), 8.78 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 8.51 (N-CH_2-**C**$\mathbf{H_3}$); 24.35(d, $J_{C,C,O,P}$ = 3.8, CH_3*i*Pr); 43.67 (C-1); 45.16 (N-**C**$\mathbf{H_2}$-CH_3); 66.74 (d, $J_{C,O,P}$ = 5.3, CH*i*Pr); 67.38 (d, $J_{C,P}$ = 155.6, CH_2P); 69.42 (d, $J_{2',P}$ = 9.8, C-2'); 130.86 (C-5); 148.17 (C-8); 148.98 (C-6); 151.53 (C-2); 152.14 (C-4). NegESI MS *m/z* (%): 333.1 (100) [M-H]; HRMS negESI ($C_{11}H_{15}ClO_4N_4P$) calculated: 333.05249; found: 333.05252.



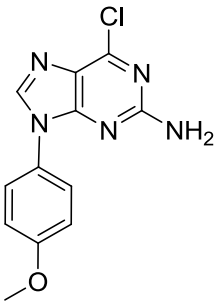
6-chloro-9-cyclohexyl-9*H*-purin-2-amine (226)

Best achieved **y**ield 191 mg (76 %). Mobile phase: 40-60% ethyl acetate in hexane. Crystallization from toluene. Spectral characteristics match those described in literature.[123a]



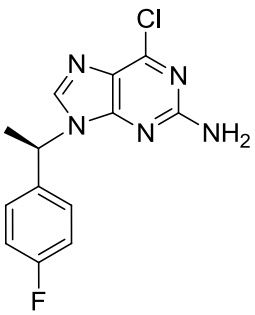
6-Chloro-9-phenyl-9*H*-purin-2-amine (242)

Best achieved **y**ield 179 mg (73 %). Mobile phase: 40-60% ethyl acetate in hexane. Crystallization from toluene. Spectral characteristics match those described in literature.[123f]



6-Chloro-9-(4-methoxyphenyl)-9*H*-purin-2-amine (243)

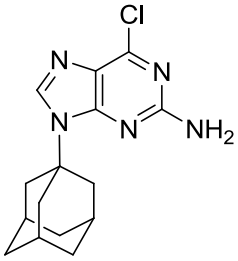
Best achieved **y**ield 221 mg (80 %). Mobile phase: 80 - 100% ethyl acetate in hexane. Crystallization from ethyl acetate. Off-white crystals, m.p. 250 - 251 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.82 (s, 3H, CH_3), 6.98 (bs, 2H, NH_2), 7.12 (m, 2H, H-3'), 7.67 (m, 2H, H-2'), 8.40 (s, 1H, H-8),. ^{13}C NMR (125.8 MHz, DMSO): δ 55.73 CH_3), 114.75 (C-3'), 123.69 (C-5), 125.57 (C-2'), 127.58 (C-1'), 142.45 (C-8), 149.98 (C-6), 154.02 (C-4), 158.94 (C-4'), 160.34 (C-2). ESI MS *m/z* (%): 276.3 (100) [M+H], 298.3 (77) [M+Na]; HRMS ESI ($C_{12}H_{11}ON_5Cl$) calculated: 276.06466; found: 276.06483. For $C_{12}H_{10}N_5ClO$ (275.69) calculated: 52.28% C, 3.66% H, 25.40% N, 12.86% Cl; found: 52.41% C, 3.68% H, 25.28% N, 12.95% Cl.



6-chloro-9-[(1*R*)-1-(4-fluorophenyl)ethyl]-9*H*-purin-2-amine (244)

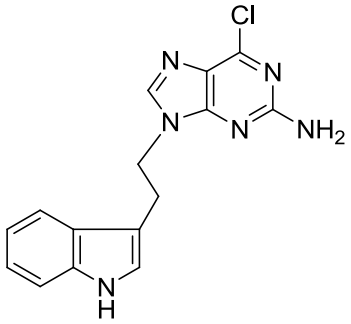
Best achieved **y**ield 271 mg (93 %). Mobile phase: 50-80% ethyl acetate in hexane. White foam on rapid evaporation from chloroform. ^{1}H NMR (500 MHz, DMSO): δ 1.90 (d, 3H, J_{CH3-CH} = 7.2, CH_3), 5.71 (q, 1H, J_{CH-CH3} = 7.2, **CH**-CH_3), 6.89 (bs, 2H, NH_2), 7.18 (m, 2H, H-3'), 7.36 (m, 2H, H-2'), 8.36 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 20.56 (CH_3), 52.77 (**CH**-CH_3), 115.63 (d,

$J_{3',F}$ = 21.5, C-3'), 123.67 (C-5), 128.48 (d, $J_{2',F}$ = 8.4, C-2'), 137.53 (d, $J_{1',F}$ = 3.1, C-1'), 141.60 (C-8), 149.66 (C-6), 153.87 (C-4), 159.86 (C-2), 161.68 (d, $J_{4',F}$ = 244.1, C-4').ESI MS *m/z* (%): 292.1 (4) [M+H], 314.1 (100) [M+Na]; HRMS ESI ($C_{13}H_{11}N_5ClFNa$) calculated: 314.05792; found: 314.05795. For $C_{13}H_{11}N_5FCl$ (291.71) calculated: 53.53% C, 3.80% H, 24.01% N, 6.51% F, 12.15% Cl; found: 53.41% C, 3.87% H, 23.99% N, 6.59% F, 12.00% Cl.



6-Chloro-9-(1-adamantyl)-9*H*-purin-2-amine (245)

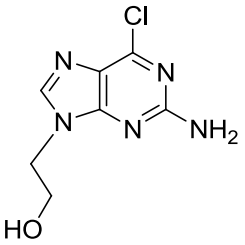
Best achieved **y**ield 200 mg (66 %). Mobile phase: 50-80% ethyl acetate in hexane. Crystallization from toluene (white crystals), m.p. 252 °C. ^{1}H NMR (500 MHz, DMSO): δ 1.73 (m, 6H, H-4'), 2.17 (m, 3H, H-3'), 2.35 (m, 6H, H-2'), 6.77 (bs, 2H, NH_2), 8.11 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 29.06 (C3'), 35.60 (C-4'), 40.47 (C-2'), 57.63 (C-1'), 124.72 (C-5), 140.62 (C-8), 149.80 (C-6), 154.17 (C-4), 158.91 (C-2). ESI MS *m/z* (%): 304.2 (100) [M+H], 326.1 (53) [M+Na]; HRMS ESI ($C_{15}H_{19}N_5Cl$) calculated: 304.13235; found: 304.13234. For $C_{15}H_{18}N_5Cl$ (303.79) calculated: 59.30% C, 5.97% H, 23.05% N, 11.67% Cl; found: 59.02% C, 6.10% H, 23.22% N, 11.60% Cl.



6-Chloro-9-[2-(1*H*-indol-3-yl)ethyl]-9*H*-purin-2-amine (246)

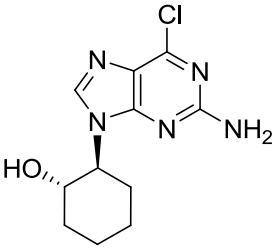
Best achieved **y**ield 303 mg (97 %). Mobile phase: 50-70% ethyl acetate in hexane. Crystallization from toluene (pale yellow crystals), m.p. 188 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.22 (m, 2H, 3'-CH_2), 4.34 (m, 2H, N-CH_2), 6.91 (bs, 2H, NH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.0, H-5'), 7.05 - 7.09 (m, 2H, H-2', H-6'), 7.34 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.53 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 7.95 (s, 1H, H-8), 10.86 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 25.08 (3'-CH_2), 43.82 (N-CH_2), 110.34 (C-3'), 111.62 (C-7'), 118.36 (C-4'), 118.59 (C-5'), 121.26 (C-6'), 123.22 (C-2'), 123.53 (C-5), 127.07 (C-3'a), 136.35 (C-7'a), 143.39 (C-8), 149.41 (C-6), 154.24 (C-4), 159.91 (C-2). ESI MS *m/z* (%): 313.1 (100) [M+H], 335.1 (94) [M+Na]; HRMS ESI ($C_{15}H_{14}N_6Cl$) calculated:

313.09630; found: 313.09633. For $C_{15}H_{13}N_6Cl$ (312.76) calculated: 57.60% C, 4.19% H, 26.87% N, 11.34% Cl; found: 57.79% C, 4.18% H, 26.92% N, 11.28% Cl.



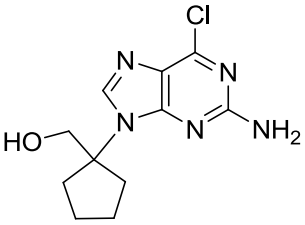
2-(2-Amino-6-chloro-9*H*-purin-9-yl)ethanol (247)

Best achieved **y**ield 192 mg (90 %). Mobile phase: 1-3% methanol in ethyl acetate. Crystallization from acetone (off-white crystals), m.p. 232 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.71 (q, 2H, $J_{2',OH} = J_{2',1'} = 5.4$, H-2'), 4.09 (t, 2H, $J_{1',2'} = 5.5$, H-1'), 5.00 (t, 1H, $J_{OH,2'} = 5.4$, OH), 6.86 (bs, 2H, NH_2), 8.06 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 45.95 (C-1'), 58.99 (C-2'), 123.55 (C-5), 143.96 (C-8), 149.35 (C-6), 154.36 (C-4), 159.86 (C-2). ESI MS *m/z* (%): 214.1 (43) [M+H], 236.1 (100) [M+Na]; HRMS ESI ($C_7H_9ON_5Cl$) calculated: 214.04901; found: 214.04906. For $C_7H_8N_5OCl$ (213.62) calculated: 39.36% C, 3.77% H, 32.78% N, 16.60% Cl; found: 39.42% C, 3.85% H, 32.91% N, 16.40% Cl.



(1*R,2*R**)-2-(2-Amino-6-chloro-9*H*-purin-9-yl) cyclohexanol (248)**

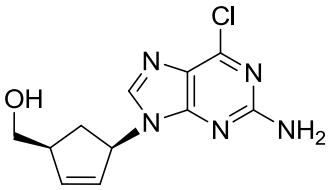
Best achieved **y**ield 219 mg (82 %). Mobile phase: 1-3% methanol in ethyl acetate. Crystallization from ethyl acetate. Spectral characteristics match those described in literature.[123g]



(1-(2-Amino-6-chloro-9*H*-purin-9-yl)cyclopentyl) methanol (249)

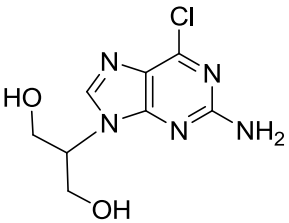
Best achieved **y**ield 177 mg (66 %). Mobile phase: 1-5% methanol in ethyl acetate. Crystallization from ethyl acetate - acetone mixture (off-white crystals), m.p. 199 °C. ^{1}H NMR (500 MHz, DMSO): δ 1.65 - 1.71 (m, 4H, H-3'), 2.13 and 2.33 (m, 2H, H-2'), 3.68 (d, 2H, $J_{CH2,OH} = 5.8$, CH_2O), 4.98 (t, 1H, $J_{OH,CH2} = 5.9$, OH), 6.74 (bs, 1H, NH_2), 8.06 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 22.64 (C-3'), 33.35 (C-2'), 63.73 (CH_2O), 70.99 (C-1'), 124.57 (C-5), 143.20 (C-8), 149.44 (C-6), 154.38 (C-4),

159.13 (C-2). ESI MS *m/z* (%): 268.1 (19) [M+H], 290.1 (100) [M+Na]; HRMS ESI ($C_{11}H_{15}ON_5Cl$) calculated: 268.09596; found: 268.09593. For $C_{11}H_{14}N_5ClO$ (267.71) calculated: 49.35% C, 5.27% H, 26.16% N, 13.24% Cl; found: 49.43% C, 5.29% H, 26.33% N, 13.36% Cl.



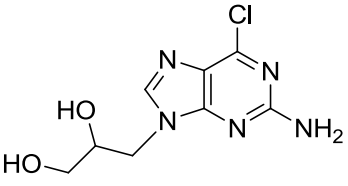
((1*S*,4*R*)-4-(2-Amino-6-chloro-9*H*-purin-9-yl) cyclopent-2-enyl)methanol (250)

Best achieved **y**ield 213 mg (80 %). Mobile phase: 3-8% methanol in ethyl acetate. Crystallization from toluene - ethyl acetate mixture. Spectral characteristics match those described in literature.[125a]



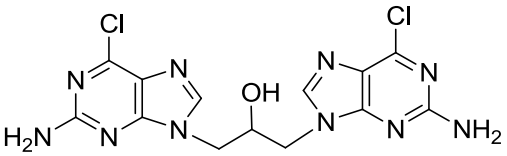
2-(2-Amino-6-chloro-9*H*-purin-9-yl)propan-1,3-diol (251)

Best achieved **y**ield 199 mg (82 %). Mobile phase: 5-10% methanol in ethyl acetate. Crystallization from ethyl acetate (white crystals), m.p. 224 °C (decomp.). ^{1}H NMR (500 MHz, DMSO): δ 3.76 (dt, 2H, J_{gem} = 11.4, $J_{2'b,1'}$ = $J_{2'b,OH}$ = 5.3, H-2'b), 3.84 (ddd, 2H, J_{gem} = 11.4, $J_{2'a,1'}$ = 7.0, $J_{2'b,OH}$ = 5.5, H-2'a), 4.42 (m, 1H, H-1'), 5.01 (t, 2H, $J_{OH,2'}$ = 5.5, OH), 6.83 (bs, 2H, NH_2), 8.11 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 59.21 (C-1'), 59.74 (C-2'), 123.65 (C-5), 142.85 (C-8), 149.28 (C-6), 154.64 (C-4), 159.66 (C-2). ESI MS *m/z* (%): 244.1 (39) [M+H], 266.1 (100) [M+Na]; HRMS ESI ($C_8H_{11}O_2N_5Cl$) calculated: 244.05958; found: 244.05949. For $C_8H_{10}N_5O_2Cl$ (243.65) calculated: 39.44% C, 4.14% H, 28.74% N, 14.55% Cl; found: 39.35% C, 4.11% H, 28.80% N, 14.67% Cl.



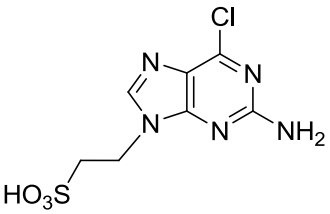
3-(2-Amino-6-chloro-9*H*-purin-9-yl)propan-1,2-diol (252)

Best achieved **y**ield 200 mg (82 %). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from ethanol - ethyl acetate mixture. Spectral characteristics match those described in literature.[123h]



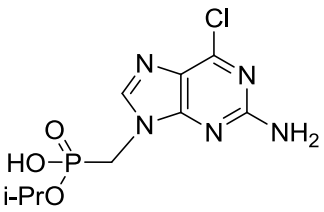
1,3-Bis(2-amino-6-chloro-9*H*-purin-9-yl)propan-2-ol (253)

Best achieved **y**ield 340 mg (86 %). Poorly soluble product was filtered off directly from the reaction mixture boiled in methanol (20 mL) and collected. Orange solid, m.p. > 350 °C. ^{1}H NMR (600 MHz, DMSO): δ 4.00 (dd, 2H, J_{gem} = 14.3, $J_{1'b,2'}$ = 8.1, H-1'b), 4.19 (dd, 2H, J_{gem} = 14.2, $J_{1'a,2'}$ = 3.5, H-1'a), 4.27 (m, 1H, H-2'), 5.60 (d, 1H, $J_{OH,2'}$ = 5.6, OH), 6.88 (bs, 4H, NH_2), 8.05 (s, 2H, H-8). ^{13}C NMR (150 MHz, DMSO): δ 47.06 (C-1'), 66.73 (C-2'), 123.43 (C-5), 144.10 (C-8), 149.43 (C-6), 154.50 (C-4), 159.90 (C-2). ESI MS *m/z* (%): 395.1 (11) [M+H], 417.1 (100) [M+Na]; HRMS ESI ($C_{13}H_{13}ON_{10}Cl_2$) calculated: 395.06454; found: 395.06444. For $C_{13}H_{12}N_{10}Cl_2O$ (395.21) calculated: 39.51% C, 3.06% H, 35.44% N, 17.94% Cl; found: 39.66% C, 3.10% H, 35.17% N, 18.02% Cl.



2-(2-Amino-6-chloro-9*H*-purin-9-yl)ethanesulfonic acid, TEA salt (254)

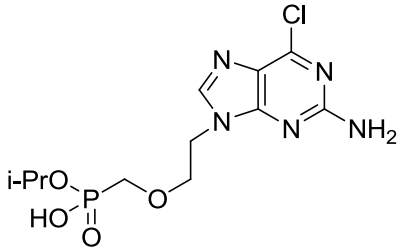
Best achieved **y**ield 273 mg (72 %). Purification on HPLC (50 mM TEAB - methanol). Light orange foam (methanol). ^{1}H NMR (500 MHz, DMSO): δ 1.17 (t, 9H, $J_{CH3,CH2}$ = 7.3, CH_3), 2.94 (m, 2H, H-2'), 3.09 (q, 6H, $J_{CH2,CH3}$ = 7.3, $\mathbf{CH_2}CH_3$), 4.29 (m, 2H, H-1'), 6.91 (bs, 2H, NH_2), 8.12 (s, 1H, H-8), 8.94 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 8.79 (CH_3), 40.42 (C-1'), 45.92 ($\mathbf{CH_2}CH_3$), 50.19 (C-2'), 123.49 (C-5), 143.96 (C-8), 149.24 (C-6), 154.17 (C-4), 159.84 (C-2). ESI MS *m/z* (%): 278.0 (45) [M+H], 379.2 (100) [M+Et_3N]; HRMS ESI ($C_7H_9O_3N_5ClS$) calculated: 278.01091; found: 278.01087.



Propan-2-yl hydrogen [(2-amino-6-chloro-9H-purin-9-yl)methyl]phosphonate, DIPEA salt (255)

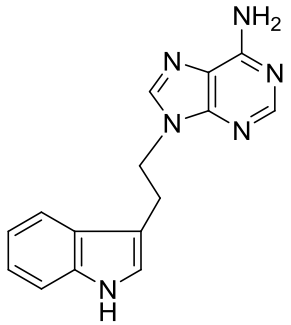
Best achieved **y**ield 318 mg (73 %). Purification on HPLC (water - methanol). Orange wax. ^{1}H NMR (500 MHz, DMSO): δ 0.97 (bs, 6H, P-O-CH-$\mathbf{CH_3}$), 1.23 - 1.27 (m, 15H, N-CH-$\mathbf{CH_3}$, N-

CH_2-**CH_3**), 3.07 (m, 2H, N-**CH_2**-CH_3), 3.54 (m, 2H, N-**CH**-CH_3), 3.97 (bs, 2H, P-CH_2), 4.21 (m, 1H, P-O-**CH**-CH_3), 6.80 (bs, 2H, NH_2), 8.21 (bs, 1H, H-8), 9.66 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 12.32 (N-CH_2-**CH_3**), 16.84 and 18.10 (N-CH-**CH_3**), 24.44 (P-O-CH-**CH_3**), 41.61 (N-**CH_2**-CH_3), 53.29 (N-**CH**-CH_3), 122.97 (C-5), 143.85 (C-8), 149.07 (C-6), 154.45 (C-4), 159.78 (C-2). negESI MS *m/z* (%): 304.0 (100) [M-H]; HRMS negESI ($C_9H_{12}ClN_5O_3P$) calculated: 304.03718; found: 304.03731.



Isopropyl (2-(2-amino-6-chloro-9*H*-purin-9-yl)ethoxy)methylphosphonate TEA salt (256)

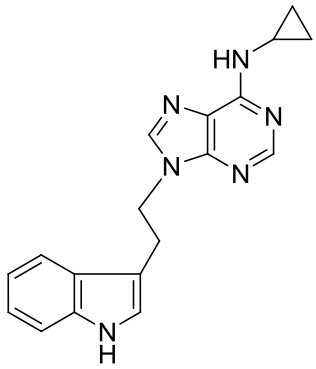
Best achieved **y**ield 194 mg (43 %). Purification on HPLC (50 mM TEAB - methanol). Orange wax. ^{1}H NMR (500 MHz, DMSO): δ 1.02 (d, 6H, $J_{CH3,CH}$ = 6.2, CH_3iPr), 1.13 (t, 9H, $J_{CH3,CH2}$ = 7.3, N-CH_2-**CH_3**), 2.93 (q, 6H, $J_{CH2,CH3}$ = 7.3, N-**CH_2**-CH_3), 3.43 (d, 2H, $J_{H,C,P}$ = 8.3, P-**CH_2**), 3.82 (m, 2H, H-2'), 4.20 (m, 2H, H-1'), 4.23 (dsept, 1H, $J_{H,C,O,P}$ = 8.2, $J_{CH,CH3}$ = 6.2, CHiPr), 6.88 (bs, 2H, NH_2), 8.16 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 8.48 (N-CH_2-**CH_3**), 24.45(d, $J_{C,C,O,P}$ = 3.7, CH_3iPr), 42.92 (C-1), 45.11 (N-**CH_2**-CH_3), 66.73 (d, $J_{C,O,P}$ = 5.6, CHiPr), 67.58 (d, $J_{C,P}$ = 156.0, CH_2P), 69.54 (d, $J_{2',P}$ = 10.1, C-2'), 123.39 (C-5), 143.85 (C-8), 149.34 (C-6), 154.27 (C-4), 159.89 (C-2). negESI MS *m/z* (%): 289.0 (100) [M-H]; HRMS negESI ($C_9H_{11}O_3N_4ClP$) calculated: 289.02628; found: 289.02611.



9-(2-(1*H*-Indol-3-yl)ethyl)-9*H*-purin-6-amine (257)

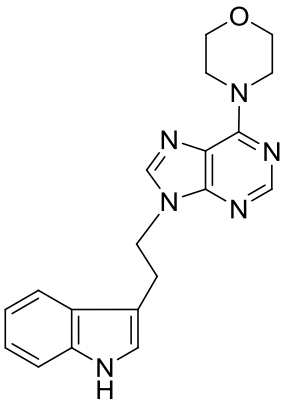
Yield 240 mg (86 %). Ethanolic ammonia was added as a 3.5 M solution (2.9 mL, 10 mmol). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from water - methanol mixture (yellow crystals), m.p. 235 °C (decomp.). ^{1}H NMR (500 MHz, DMSO): δ 3.25 (m, 2H, 3'-CH_2), 4.42 (m, 2H, N-CH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.05 - 7.08 (m, 2H, H-2', H-6'), 7.15 (bs, 2H, NH_2), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.55 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 7.99 (s, 1H, H-8), 8.18 (s, 1H, H-2), 10.84 (bs,

1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 25.63 (3'-CH_2), 43.80 (N-CH_2), 110.54 (C-3'), 111.60 (C-7'), 118.36 (C-4'), 118.56 (C-5'), 118.94 (C-5), 121.22 (C-6'), 123.20 (C-2'), 127.14 (C-3'a), 136.36 (C-7'a), 140.96 (C-8), 149.70 (C-4), 152.54 (C-2), 156.10 (C-6). ESI MS *m/z* (%): 279.4 (100) [M+H], 301.3 (39) [M+Na]; HRMS ESI ($C_{15}H_{15}N_5$) calculated: 279.13527; found: 279.13539. For $C_{15}H_{14}N_6$ (278.31) calculated: 64.73% C, 5.07% H, 30.20% N; found: 64.53% C, 5.00% H, 30.41% N.



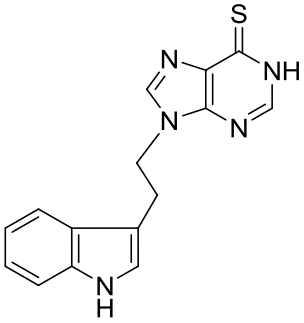
9-(2-(1*H*-Indol-3-yl)ethyl)-*N*^{6}-cyclopropyl-9*H*-purin-6-amine (258)

Yield 290 mg (91 %). Cyclopropylamine was added neat (346 μL, 5 mmol). Mobile phase: 5-10% methanol in ethyl acetate. Crystallization from toluene - cyclohexane mixture (pale brown crystals), m.p. 180-181 °C. ^{1}H NMR (500 MHz, DMSO): δ 0.61 and 0.71 (m, 4H, CH_2-cyclop), 3.05 (bs, 1H, CH-cyclop), 3.25 (m, 2H, 3'-CH_2), 4.43 (m, 2H, N-CH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.05 - 7.09 (m, 2H, H-2', H-6'), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.56 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 7.80 (m, 1H, 6-NH), 8.00 (s, 1H, H-8), 8.28 (bs, 1H, H-2), 10.84 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.59 (CH_2-cyclop), 24.2 (CH-cyclop), 25.64 (3'-CH_2), 43.77 (N-CH_2), 110.52 (C-3'), 111.60 (C-7'), 118.36 (C-4'), 118.56 (C-5'), 119.29 (C-5), 121.23 (C-6'), 123.20 (C-2'), 127.14 (C-3'a), 136.36 (C-7'a), 140.78 (C-8), 149.3 (C-4), 152.45 (C-2), 155.67 (C-6). ESI MS *m/z* (%): 319.4 (100) [M+H], 341.4 (4) [M+Na]; HRMS ESI ($C_{18}H_{19}N_6$) calculated: 319.16657; found: 319.16674. For $C_{18}H_{18}N_6$ (318.38) calculated: 67.90% C, 5.70% H, 26.40% N; found: 67.97% C, 5.72% H, 26.35% N.



9-(2-(1*H*-Indol-3-yl)ethyl)-6-morpholino-9*H*-purine (259)

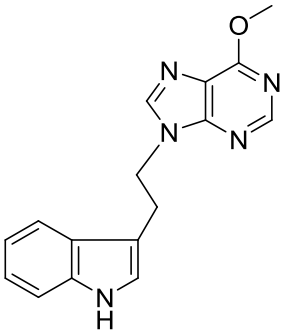
Yield 303 mg (87 %). Morpholine was added neat (437 μL, 5 mmol). Mobile phase: 1-2% methanol in ethyl acetate. Crystallization from toluene (pale yellow crystals), m.p. 194-197 °C. ^{1}H NMR (600 MHz, DMSO): δ 3.25 (m, 2H, 3'-CH_2), 3.71 (m, 4H, O-CH_2), 4.19 (bs, 4H, O-CH_2-**CH_2**), 4.45 (m, 2H, 9-CH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.06 - 7.09 (m, 2H, H-2', H-6'), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.56 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 8.06 (s, 1H, H-8), 8.30 (s, 1H, H-2), 10.84 (bs, 1H, H-1'). ^{13}C NMR (150 MHz, DMSO): δ 25.48 (3'-CH_2), 43.80 (N-CH_2), 66.32 (O-CH_2), 110.41 (C-3'), 111.57 (C-7'), 118.31 (C-4'), 118.53 (C-5'), 119.31 (C-5), 121.20 (C-6'), 123.21 (C-2'), 127.11 (C-3'a), 136.35 (C-7'a), 140.29 (C-8), 150.82 (C-4), 151.85 (C-2), 153.39 (C-6). ESI MS *m/z* (%): 349.4 (100) [M+H], 371.4 (26) [M+Na]; HRMS ESI ($C_{19}H_{20}ON_6Na$) calculated: 371.15908; found: 371.15913. For $C_{19}H_{20}N_6O$ (348.40) calculated: 65.50% C, 5.79% H, 24.12% N; found: 65.44% C, 5.81% H, 24.33% N.



9-(2-(1*H*-Indol-3-yl)ethyl)-1*H*-purin-6(9*H*)-thione (260)

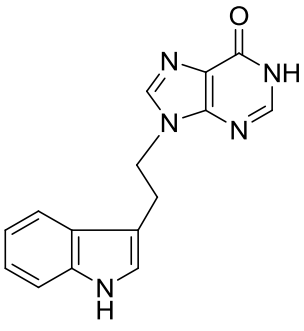
Yield 237 mg (80 %). Thiourea was added neat (152 mg, 2 mmol). Mobile phase: 1-10% methanol in ethyl acetate. Crystallization from ethanol (white crystals), m.p. 305 °C (decomp.). ^{1}H NMR (600 MHz, DMSO): δ 3.25 (m, 2H, 3'-CH_2), 4.44 (m, 2H, N-CH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 6.9, $J_{5',7'}$ = 1.1, H-5'), 7.05 - 7.08 (m, 2H, H-2', H-6'), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.55 (dm, 1H, $J_{4',5'}$ = 7.8, H-4'), 8.14 (s, 1H, H-8), 8.20 (s, 1H, H-2), 10.84 (bs, 1H, H-1'), 13.66 (bs, 1H, H-1). ^{13}C NMR (150 MHz, DMSO): δ 25.58 (3'-CH_2), 44.25 (N-CH_2), 110.11 (C-3'), 111.59 (C-7'), 118.23 (C-4'), 118.55 (C-5'), 121.21 (C-6'), 123.31 (C-2'), 127.01 (C-3'a), 135.11 (C-5), 136.34 (C-7'a), 143.13 (C-8), 144.21 (C-4), 144.91 (C-2), 175.87 (C-6). ESI MS *m/z* (%): 296.2 (100) [M+H], 318.2 (69) [M+Na]; HRMS ESI ($C_{15}H_{14}N_5S$) calculated: 296.09644; found: 296.09650. For

$C_{15}H_{13}N_5S$ (295.36) calculated: 61.00% C, 4.44% H, 23.71% N, 10.86% S; found: 61.14% C, 4.51% H, 23.92% N, 10.66% S.



9-(2-(1*H*-Indol-3-yl)ethyl)-6-methoxy-9*H*-purine (261)

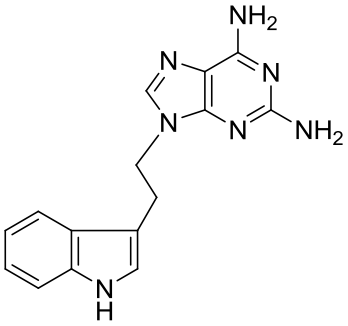
Yield 241 mg (82 %). Sodium methoxide was added as a 1 M solution in water (5 mL, 5 mmol). Mobile phase: 1-2% methanol in ethyl acetate. Crystallization from toluene (white crystals), m.p. 173 - 174 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.28 (m, 2H, 3'-CH_2), 4.09 (s, 3H, CH_3), 4.52 (m, 2H, N-CH_2), 6.97 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.0, H-5'), 7.05 - 7.08 (m, 2H, H-2', H-6'), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.53 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 8.23 (s, 1H, H-8), 8.55 (s, 1H, H-2), 10.84 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 25.47 (3'-CH_2), 44.27 (N-CH_2), 53.98 (O-CH_3), 110.27 (C-3'), 111.61 (C-7'), 118.27 (C-4'), 118.58 (C-5'), 120.74 (C-5), 121.24 (C-6'), 123.29 (C-2'), 127.08 (C-3'a), 136.35 (C-7'a), 143.94 (C-8), 151.55 (C-2), 152.22 (C-4), 160.36 (C-6). ESI MS *m/z* (%): 294.1 (71) [M+H], 316.1 (100) [M+Na]; HRMS ESI ($C_{16}H_{15}ON_5Na$) calculated: 316.11688; found: 316.11689. For $C_{16}H_{15}N_5O$ (293.32) calculated: 65.52% C, 5.15% H, 23.88% N; found: 65.29% C, 5.11% H, 24.11% N.



9-(2-(1*H*-Indol-3-yl)ethyl)-1*H*-purin-6(9*H*)-one (262)

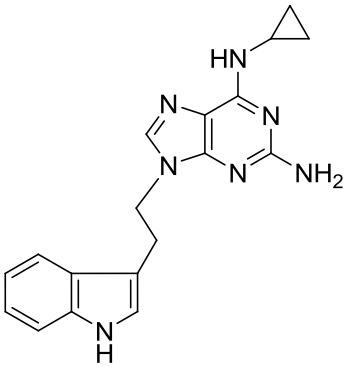
Yield 220 mg (79 %). Sodium hydroxide was added as a 2 M solution in water (5 mL, 10 mmol). Mobile phase: 10-25% methanol in ethyl acetate. Crystallization from ethylacetate - ethanol mixture. (white crystals), m.p. 214 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.26 (m, 2H, 3'-CH_2), 4.47 (m, 2H, N-CH_2), 6.97 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.07 (ddd, 1H, $J_{6',7'}$ = 8.1, $J_{6',5'}$ = 7.0, $J_{6',4'}$ = 1.2, H-6'), 7.09 (dm, 1H, $J_{2',1'}$ = 2.4, H-2'), 7.34 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.52 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 8.18 (s, 1H, H-2), 8.47 (s, 1H, H-8), 10.92 (bs, 1H, H-1'), 12.67 (bs, 1H, H-1). ^{13}C NMR (125.8 MHz, DMSO): δ 25.54 (3'-CH_2), 44.97 (N-CH_2), 109.91 (C-3'), 111.67 (C-7'), 118.18 (C-4'), 118.61 (C-5'), 121.20 (C-5), 121.28 (C-6'), 123.45 (C-2'), 127.04 (C-3'a), 136.37 (C-7'a), 140.21 (C-8), 146.93 (C-2), 148.01 (C-4), 155.59 (C-6). ESI

MS *m/z* (%): 280.2 (2) [M+H], 302.1 (100) [M+Na]; HRMS ESI ($C_{15}H_{13}ON_5Na$) calculated: 302.10123; found: 302.10115. For $C_{15}H_{13}N_5O$ (279.30) calculated: 64.51% C, 4.69% H, 25.07% N; found: 64.66% C, 4.78% H, 24.79% N.



9-[2-(1*H*-Indol-3-yl)ethyl]-9*H*-purin-2,6-diamine (263)

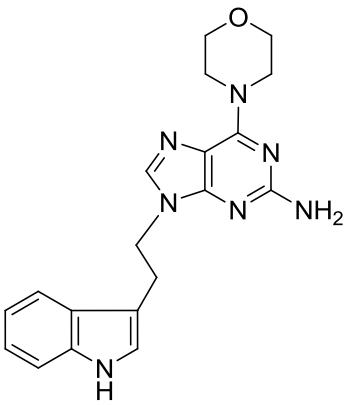
Yield 268 mg (82 %). Ethanolic ammonia was added as a 3.5 M solution (2.9 mL, 10 mmol). Poorly soluble product was filtered off directly from the reaction mixture and washed succesively with water (3 x 5 mL) and methanol (3 x 5mL). Pale red solid, m.p. 318 °C (decomp.). ^{1}H NMR (500 MHz, DMSO): δ 3.18 (m, 2H, 3'-CH_2), 4.24 (m, 2H, N-CH_2), 5.80 (bs, 2H, NH_2), 6.62 (bs, 2H, 6-NH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.06 - 7.09 (m, 2H, H-2', H-6'),7.34 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.56 (s, 1H, H-8), 7.56 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 10.84 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 25.59 (3'-CH_2), 43.15 (N-CH_2), 110.82 (C-3'), 111.58 (C-7'), 113.42 (C-5), 118.48 (C-4'), 118.56 (C-5'), 121.22 (C-6'), 123.05 (C-2'), 127.18 (C-3'a), 136.36 (C-7'a), 137.64 (C-8), 151.94 (C-4), 156.26 (C-6), 160.41 (C-2). ESI MS *m/z* (%): 294.1 (100) [M+H], 316.1 (63) [M+Na]; HRMS ESI ($C_{15}H_{16}N_7$) calculated: 294.14617; found: 294.14619. For $C_{15}H_{15}N_7$ (293.33) calculated: 61.42% C, 5.15% H, 33.43% N; found: 61.30% C, 5.17% H, 33.70% N.



9-(2-(1*H*-Indol-3-yl)ethyl)-N^6-cyclopropyl-9*H*-purin-2,6-diamine (264)

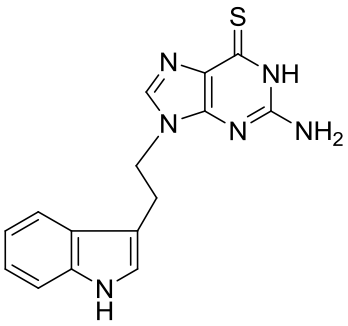
Yield 274 mg (82 %). Cyclopropylamine was added neat (346 μL, 5 mmol). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from small amount of ethyl acetate (off-white crystals), m.p. 203 °C (decomp.). ^{1}H NMR (500 MHz, DMSO): δ 0.58 and 0.65 (m, 4H, CH_2-cyclop), 3.04 (bs, 1H, CH-cyclop), 3.17 (m, 2H, 3'-CH_2), 4.25 (m, 2H, N-CH_2), 5.84 (bs, 2H, NH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.0, H-5'), 7.06 - 7.09 (m, 2H, H-2', H-6'), 7.21 (m, 1H, NH), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1,

H-7'), 7.55 (s, 1H, H-8), 7.56 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 10.83 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.59 (CH_2-cyclop), 25.60 (3'-CH_2), 43.08 (N-CH_2), 110.81 (C-3'), 111.56 (C-7'), 113.64 (C-5), 118.48 (C-4'), 118.55 (C-5'), 121.21 (C-6'), 123.04 (C-2'), 127.17 (C-3'a), 136.35 (C-7'a), 137.34 (C-8), 151.5 (C-4), 156.04 (C-6), 160.33 (C-2). ESI MS *m/z* (%): 334.2 (100) [M+H], 356.2 (16) [M+Na]; HRMS ESI ($C_{18}H_{20}N_7$) calculated: 334.17747; found: 334.17748. For $C_{18}H_{19}N_7$ (333.39) calculated: 64.85% C, 5.74% H, 29.41% N; found: 64.62% C, 5.79% H, 29.65% N.



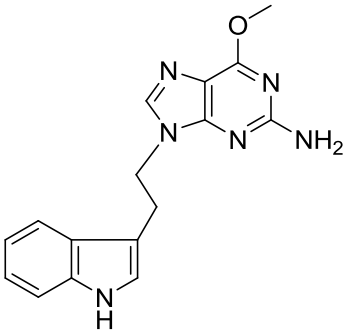
9-(2-(1*H*-Indol-3-yl)ethyl)-6-morpholino-9*H*-purin-2-amine (265)

Yield 301 mg (83 %). Morpholine was added neat (437 μL, 5 mmol). Mobile phase: 1-5% methanol in ethyl acetate. Crystallization from small amount of toluene (white crystals), m.p. 200 - 201 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.17 (m, 2H, 3'-CH_2), 3.67 (m, 4H, O-CH_2), 4.10 (bs, 4H, O-CH_2-**CH_2**), 4.27 (m, 2H, 9-CH_2), 5.93 (bs, 2H, NH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 6.9, $J_{5',7'}$ = 1.0, H-5'), 7.06 - 7.09 (m, 2H, H-2', H-6'), 7.34 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.56 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 7.61 (s, 1H, H-8), 10.84 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 25.45 (3'-CH_2), 43.12 (9-CH_2), 45.12 (O-CH_2-**CH_2**), 66.42 (O-CH_2), 110.72 (C-3'), 111.57 (C-7'), 113.64 (C-5), 118.48 (C-4'), 118.55 (C-5'), 121.22 (C-6'), 123.08 (C-2'), 127.16 (C-3'a), 136.35 (C-7'a), 137.07 (C-8), 153.28 (C-4), 153.84 (C-6), 159.69 (C-2). ESI MS *m/z* (%): 364.2 (100) [M+H], 386.2 (10) [M+Na]; HRMS ESI ($C_{19}H_{22}ON_7$) calculated: 364.18803; found: 364.18799. For $C_{19}H_{21}N_7O$ (363.42) calculated: 62.79% C, 5.82% H, 26.98% N; found: 62.73% C, 5.86% H, 26.70% N.



9-(2-(1*H*-Indol-3-yl)ethyl)-2-amino-1H-purin-6(9*H*)-thione (266)

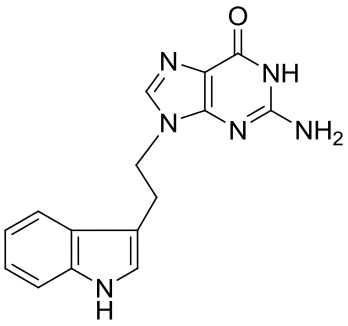
Yield 262 mg (84 %). Thiourea was added neat (152 mg, 2 mmol). Mobile phase: 2-8% methanol in ethyl acetate. Crystallization from small amount of ethanol (white crystals), m.p. 325 °C (decomp.). ^{1}H NMR (600 MHz, DMSO): δ 3.18 (m, 2H, 3'-CH_2), 4.25 (m, 2H, N-CH_2), 6.80 (bs, 2H, NH_2), 6.99 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 6.9, $J_{5',7'}$ = 1.0, H-5'), 7.06 - 7.09 (m, 2H, H-2', H-6'), 7.34 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.56 (dm, 1H, $J_{4',5'}$ = 7.8, H-4'), 7.74 (s, 1H, H-8), 10.85 (bs, 1H, H-1'), 11.86 (bs, 1H, H-1). ^{13}C NMR (150 MHz, DMSO): δ 25.33 (3'-CH_2), 43.51 (N-CH_2), 110.37 (C-3'), 111.59 (C-7'), 118.37 (C-4'), 118.57 (C-5'), 121.23 (C-6'), 123.17 (C-2'), 127.05 (C-3'a), 128.34 (C-5), 136.35 (C-7'a), 140.65 (C-8), 147.94 (C-4), 153.08 (C-2), 174.91 (C-6). ESI MS *m/z* (%): 311.1 (62) [M+H], 333.1 (100) [M+Na]; HRMS ESI ($C_{15}H_{14}N_6NaS$) calculated: 333.08929; found: 333.08928. For $C_{15}H_{14}N_6S$ (310.38) calculated: 58.38% C, 4.55% H, 27.08% N, 10.33% S; found: 58.47% C, 4.52% H, 26.95% N, 10.52% S.



9-(2-(1*H*-Indol-3-yl)ethyl)-6-methoxy-9*H*-purin-2-amine (267)

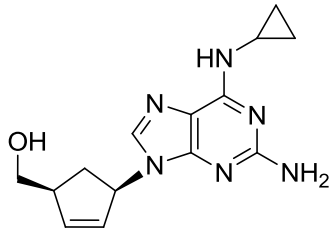
Yield 286 mg (93 %). Sodium methoxide was added as a 1 M solution in water (5 mL, 5 mmol). Mobile phase: 2-5% methanol in ethyl acetate. Crystallization from toluene (white crystals), m.p. 178 - 179 °C. ^{1}H NMR (500 MHz, DMSO): δ 3.19 (m, 2H, 3'-CH_2), 3.95 (s, 3H, CH_3), 4.30 (m, 2H, N-CH_2), 6.42 (bs, 2H, NH_2), 6.98 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 7.0, $J_{5',7'}$ = 1.1, H-5'), 7.05 - 7.09 (m, 2H, H-2', H-6'), 7.33 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.55 (dm, 1H, $J_{4',5'}$ = 7.9, H-4'), 7.69 (s, 1H, H-8), 10.84 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 25.38 (3'-CH_2), 43.45 (N-CH_2), 53.24 (O-CH_3), 110.59 (C-3'), 111.58 (C-7'), 113.97 (C-5), 118.42 (C-4'), 118.57 (C-5'), 121.23 (C-6'), 123.10 (C-2'), 127.13 (C-3'a), 136.34 (C-7'a), 139.92 (C-8), 154.30 (C-4), 159.92 (C-2), 160.77 (C-6). ESI MS *m/z* (%): 309.2 (66) [M+H], 331.1 (100) [M+Na]; HRMS ESI ($C_{16}H_{17}ON_6$) calculated: 309.14584; found: 309.14583. For

$C_{16}H_{16}N_6O$ (308.34) calculated: 62.32% C, 5.23% H, 27.26% N; found: 62.46% C, 5.12% H, 27.19% N.



9-(2-(1*H*-Indol-3-yl)ethyl)-2-amino-1*H*-purin-6(9*H*)-on (268)

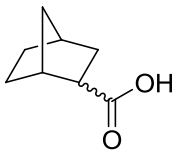
Yield 259 mg (88 %). Sodium hydroxide was added as a 2 M solution in water (5 mL, 10 mmol). Poorly soluble product was filtered off, boiled with methanol-water mixture (2:1) and collected again. Pale red solid, m.p. 354 °C (decomp.). ^{1}H NMR (500 MHz, DMSO): δ 3.18 (m, 2H, 3'-CH_2), 4.25 (m, 2H, N-CH_2), 6.80 (bs, 2H, NH_2), 6.99 (ddd, 1H, $J_{5',4'}$ = 7.9, $J_{5',6'}$ = 6.9, $J_{5',7'}$ = 1.0, H-5'), 7.06 - 7.09 (m, 2H, H-2', H-6'), 7.34 (dm, 1H, $J_{7',6'}$ = 8.1, H-7'), 7.56 (dm, 1H, $J_{4',5'}$ = 7.8, H-4'), 7.74 (s, 1H, H-8), 10.85 (bs, 1H, H-1'), 11.86 (bs, 1H, H-1). ^{13}C NMR (125.8 MHz, DMSO): δ 25.33 (3'-CH_2), 43.51 (N-CH_2), 110.37 (C-3'), 111.59 (C-7'), 118.37 (C-4'), 118.57 (C-5'), 121.23 (C-6'), 123.17 (C-2'), 127.05 (C-3'a), 128.34 (C-5), 136.35 (C-7'a), 140.65 (C-8), 147.94 (C-4), 153.08 (C-2), 174.91 (C-6). ESI MS *m/z* (%): 295.1 (40) [M+H], 317.1 (100) [M+Na]; HRMS ESI ($C_{15}H_{12}ON_6$) calculated: 295.13019; found: 295.13015. For $C_{15}H_{14}N_6O$ (294.31) calculated: 61.21% C, 4.79% H, 28.55% N; found: 61.47% C, 4.81% H, 28.34% N.



((1*S*,4*R*)-4-(2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl)cyclopent-2-enyl)methanol (39)

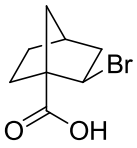
A crude reaction mixture of **250** (starting from 1 mmol of **98**) was treated with cyclopropylamine analogously to the general method **B**. Mobile phase: 5-15% methanol in ethyl acetate. Yield 215 mg (75 %). Crystallization from a small amount of ethyl acetate. Spectral characteristics match those described in literature.[125a]

5.5. Carbocyclic nucleoside analogues locked in North conformation



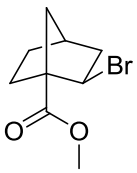
(1*S,4*R**)-Bicyclo[2.2.1]heptane-2-carboxylic acid (273)**

A mixture of dicyclopentadiene (165 g, 1.25 mol DCPD), ethyl acrylate (250 g, 2.5 mol) and hydroquinone (5 g) was heated in autoclave at 180°C for 4 hours. To the resulting solution of crude **271** was added dry methanol (200 mL) and $Pd(OH)_2/C$ (3 g) and the mixture was hydrogenated (100 atm) until the consumption of the hydrogen ceased. Catalyst was filtered off on a pad of cellite, the solution of crude **272** was diluted with methanol (1 L), solution of NaOH (250 g, 800 mL of H_2O) was added and the mixture was stirred at RT overnight. Methanol was evaporated, water solution was diluted to approx 3 L and washed with ethyl acetate (2 x 700 mL). Water layer was acidified with conc. HCl to pH = 3 and product was extracted with ethyl acetate (3 x 1 L). Organic extracts were dried over sodium sulfate, evaporated and distilled at reduced pressure (170°C, 17 mbar) to give **273** (mixture of stereoisomers) as a colorless oil (284,3 g, 82,3% over three steps). Spectral characteristics match those described in literature.[145]



(1*S,2*S**,4*R**)-2-Bromobicyclo[2.2.1]heptane-1-carboxylic acid (274)**[127]

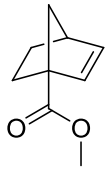
A mixture of **273** (284.3 g, 2,058 mol), bromine (127 mL, 2.47 mol) and PCl_3 (10 mL) was heated to 90°C for 3 days under reflux condenser. Reaction mixture (solidifies on cooling) was dissolved in ethyl acetate (3 L) and washed with water (2 x 0.7 L), saturated sodium thiosulfate (2 x 0.7 L) and water (2 x 0.7 L). Organic phase was dried over sodium sulfate and evaporated. The residue was crystallized from toluene to provide 216 g of **274** as colorless needles. Mother liquour was further crystallized from toluene-hexane mixture, to provide another 63 and 23 g of **274** as white powder (total 302 g, 67%). Spectral characteristics match those described in literature.[146]



Methyl (1*S,2*S**,4*R**)-2-bromobicyclo[2.2.1]heptane-1-carboxylate (275)**

Concentrated H_2SO_4 (18 mL) was added dropwise to a solution of **274** (130 g, 0.594 mol) in dry methanol (800 mL) and this mixture was heated to

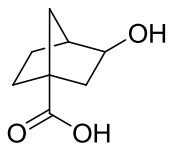
reflux for 12 hours. After it cooled down the solution was neutralized with $NaHCO_3$ (40 g), methanol was evaporated and the solution of the residue in ethyl acetate (1.5 L) was washed with water (2 x 500 mL), dried with sodium sulfate and evaporated. Distillation under reduced pressure (130°C, 2 mbar) afforded **275** (130 g, 94%) as colorless liquid. Spectral characteristics match those described in literature.[147]



Methyl (1*R,4*R**)-bicyclo[2.2.1]hept-2-ene-1-carboxylate (277)**

A solution of bromoester **275** (117 g, 0.502 mol) and DBU (186 mL, 1.25 mol) in DMF (700 mL) was heated to 110°C for 48 h. Reaction mixture was diluted with water (3 L) and extracted with hexane (4 x 800 mL). Organic extracts were dried with sodium sulfate and evaporated. Crude product (80% purity on GCMS) was distilled under reduced pressure to afford **277** (42 g, 55%) as a colorless oil.

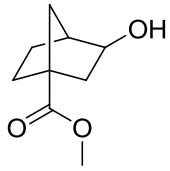
^{1}H NMR (500 MHz, DMSO): 1.03 (dm, 1H, J_{gem} = 11.0, H-5endo), 1.24 (ddd, 1H, J_{gem} = 11.1, $J_{6en,5ex}$ = 3.6, $J_{6en,7'}$ = 2.4, H-6endo), 1.43 (dm, 1H, J_{gem} = 8.1, H-7b), 1.47 (dm, 1H, J_{gem} = 8.1, H-7a), 1.83 (ddd, 1H, J_{gem} = 11.0, $J_{5ex,6ex}$ = 9.4, $J_{5ex,6en}$ = 3.6, H-5exo), 1.92 (ddd, 1H, J_{gem} = 11.1, $J_{6ex,5ex}$ = 9.4, $J_{6ex,5en}$ = 3.8, H-6exo), 2.93 (m, 1H, H-4), 3.67 (s, 3H, CH_3), 6.10 (d, 1H, $J_{2,3}$ = 5.6, H-2), 6.13 (dd, 1H, $J_{3,2}$ = 5.6, $J_{3,4}$ = 3.0, H-3), ^{13}C NMR (125.8 MHz, DMSO): 25.95 (C-5), 29.47 (C-6), 42.35 (C-4), 51.52 (C-7), 51.76 (CH_3), 57.47 (C-1), 134.21 (C-2), 136.33 (C-3), 174.48 (COO). ESI MS *m/z* (%): 153.1 (100) [M+H]; HRMS ESI ($C_9H_{13}O_2$) calculated: 153.09101; found: 153.09107. For $C_9H_{12}O_2$ (152.19) calculated: 71.03% C, 7.95% H; found: 71.30% C, 7.99% H.



(1*R,3*R**,4*R**)-3-Hydroxybicyclo[2.2.1]heptane-1-carboxylic acid (278)**

Mercuric acetate (20 g, 63 mmol) was dissolved in a THF (120 mL) - water (60 mL) mixture and a solution of **277** (9.1 g, 60 mmol) in THF (10 mL) was added dropwise. After 30 minutes a 3M solution of NaOH (60 mL) was added and after another 30 minutes a solution of $NaBH_4$ (1.2 g, 32 mmol) in 3M NaOH (60 mL) was added. Elemental mercury was separated in a separatory funnel, organic layer was separated set aside and water layer was then extracted with ethyl acetate (3 x 60 mL). Organic extracts were connected, dried over sodium sulphate and evaporated.

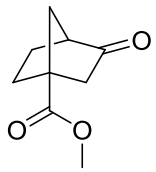
Crude product was crystallized from benzene to provide pure **278** (6.3 g, 67%) as colorless crystals. Spectral characteristics match those described in literature.[128]



Methyl (1*S,3*S**,4*S**)-3-hydroxybicyclo[2.2.1]heptane-1-carboxylate (279)**

To a solution of **278** (6.3 g, 40.2 mmol) in diethylether (100 mL) 1M solution of diazomethane was added dropwise, until nitrogen ceased evolving and the solution acquired a slightly yellow color. Diethylether was evaporated to afford **279** (6.8 g, 99%) as a colorless oil.

^{1}H NMR (500 MHz, DMSO): 1.09 (ddddd, 1H, J_{gem} = 12.2, $J_{5en-6en}$ = 9.1, J_{5en-4} = $J_{5en-6ex}$ = 4.8, J_{5en-7} = 2.1, H-5endo), 1.29 (dddd, 1H, J_{gem} = 11.6, $J_{6en-5en}$ = 9.2, $J_{6en-5ex}$ = 4.0, J_{6en-7} = 2.3, H-6endo), 1.35 (dm, 1H, J_{gem} = 9.5, H-7b), 1.51 (dm, 1H, J_{gem} = 12.8, H-2exo), 1.56 (dm, 1H, J_{gem} = 12.2, H-5exo), 1.68 (m, 1H, H-6exo), 1.80 (ddd, 1H, J_{gem} = 12.8, J_{2en-3} = 6.8, J_{2en-7a} = 2.3, H-2endo), 1.82 (dm, 1H, J_{gem} = 9.5, H-7a), 2.07 (d, 1H, J_{4-6ex} = 4.8, H-4), 3.60 (s, 3H, CH_3), 3.66 (dm, 1H, J_{3-2en} = 6.6, H-3), 4.69 (d, 1H, OH). ^{13}C NMR (125.8 MHz, DMSO): 24.41 (C-5), 31.74 (C-6), 38.24 (C-7), 44.69 (C-2), 44.81 (C-4), 50.88 (C-1), 51.57 (CH_3), 73.11 (C-3), 175.49 (COO). ESI MS *m/z* (%): 171.1 (21) [M+H], 193.1 (100) [M+Na]; HRMS ESI ($C_9H_{14}O_3Na$) calculated: 193.08352 found: 193.08361. For $C_9H_{14}O_3$ (170.21) calculated: 63.51% C, 8.29% H; found: 63.77% C, 8.32% H.

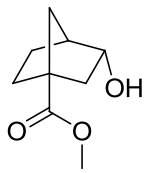


Methyl (1*S,4*S**)-3-oxobicyclo[2.2.1]heptane-1-carboxylate (280)**

Alcohol **279** (6.8 g, 40 mmol) was dissolved in dichloromethane (20 mL) and added dropwise to a vigorously stirred suspension of PDC (22.7 g, 60 mmol) and crushed molecular sieves (23 g) in dichloromethane (200 mL). Reaction mixture was stirred at RT overnight, solids were filtered off on a cellite pad and solvent was evaporated. Resulting dark-brown slurry was filtered through a plug of silica gel (toluene - ethyl acetate 4:1) to afford ketone **280** (5.57 g, 82%) as a colorless oil.

^{1}H NMR (500 MHz, DMSO): 1.43 (m, 1H, H-5endo), 1.70 (m, 1H, H-6exo), 1.83 (ddd, 1H, J_{gem} = 10.1, $J_{7b,4}$ = 4.2, $J_{7b,3en}$ = 1.2, H-7b), 1.93 (dm, 1H, J_{gem} = 10.1, H-7a), 1.96 (m, 1H, J_{gem} = 12.8, H-5exo), 2.01 (m, 1H, H-6endo), 2.12 (dm, 1H, J_{gem} = 17.8, H-2endo), 2.38 (dm, 1H, J_{gem} = 17.8, H-2exo), 2.59 (dm, 1H, J_{4-6ex} = 4.7, H-4), 3.66 (s, 3H, CH_3). ^{13}C NMR (125.8 MHz, DMSO): 23.95 (C-5), 30.58 (C-6), 40.25

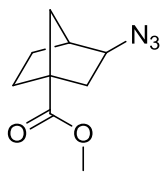
(C-7), 46.65 (C-2), 50.46 (C-1), 50.55 (C-4), 51.99 (CH_3), 173.69 (C-3), 213.48 (COO). ESI MS *m/z* (%): 169.1 (2) [M+H], 191.1 (100) [M+Na]; HRMS ESI ($C_9H_{12}O_3Na$) calculated: 193.08352 found: 193.08358. For $C_9H_{12}O_3$ (168.19) calculated: 64.27% C, 7.19% H; found: 64.18% C, 7.24% H.



Methyl (1*R,3*S**,4*R**)-3-hydroxybicyclo[2.2.1]heptane-1-carboxylate (281)**

$NaBH_4$ was added portionwise to a solution of ketone **280** (5.57 g, 33 mmol) in dry methanol (100 mL) at 0°C and this solution was stirred at RT overnight. Methanol was evaporated and the residue was partitioned between brine and ethyl acetate. Water phase was further extracted with ethyl acetate (2 x 100 mL), connected organic layers were dried over sodium sulfate and evaporated. After codistilation with methanol (3 x 50 mL), **281** (4.96 g, 88%) was acquired as a colorless oil.

^{1}H NMR (500 MHz, DMSO): 1.03 (dm, 1H, J_{gem} = 12.5, H-2endo), 1.29 (dddd, 1H, J_{gem} = 11.6, $J_{6en-5en}$ = 9.2, $J_{6en-5ex}$ = 4.0, J_{6en-7} = 2.3, H-6endo), 1.35 (dm, 1H, J_{gem} = 9.5, H-7b), 1.51 (dm, 1H, J_{gem} = 12.8, H-2exo), 1.56 (dm, 1H, J_{gem} = 12.2, H-5exo), 1.68 (m, 1H, H-6exo), 1.80 (ddd, 1H, J_{gem} = 12.8, J_{2en-3} = 6.8, J_{2en-7a} = 2.3, H-2endo), 1.82 (dm, 1H, J_{gem} = 9.5, H-7a), 2.07 (d, 1H, J_{4-5ex} = 4.8, H-4), 3.60 (s, 3H, CH_3), 3.66 (dm, 1H, J_{3-2en} = 6.6, H-3), 4.69 (d, 1H, OH). ^{13}C NMR (125.8 MHz, DMSO): 24.41 (C-5), 31.74 (C-6), 38.24 (C-7), 44.69 (C-2), 44.81 (C-4), 50.88 (C-1), 51.57 (CH_3), 73.11 (C-3), 175.49 (COO). ESI MS *m/z* (%): 171.1 (5) [M+H], 193.1 (100) [M+Na]; HRMS ESI ($C_9H_{14}O_3Na$) calculated: 193.08352 found: 193.08358. For $C_9H_{14}O_3$ (170.21) calculated: 63.51% C, 8.29% H; found: 63.56% C, 8.41% H.



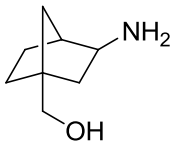
(1*R,3*S**,4*S**)-Methyl 3-azidobicyclo[2.2.1]heptane-1-carboxylate (283)**

Mesylchloride (4.2 mL, 53 mmol) was added to a solution of **281** (6.9 g, 41 mmol) in dry pyridine at 0°C. Reaction mixture was stirred at RT for 3 hours, quenched with water and partitioned between water (100 mL) and ethyl acetate (300 mL). Organic phase was then washed with dil. HCl (2 x 50 mL), $NaHCO_3$ (2 x 50 mL) and water, dried with sodium sulfate and evaporated. Acquired

282 (10 g, 99%, > 98% pure on GCMS analysis) was directly used to the next reaction.

Sodium azide (7.8 g, 120 mmol) was added to a solution of mesylate **282** (10 g, 40 mmol) in DMF (150 mL) and the reaction mixture was heated to 115°C overnight. After evaporation of DMF, crude product was partitioned between water (100 mL) and ethyl acetate (300 mL). Organic phase was washed with water (2 x 100 mL), dried with sodium sulfate and evaporated. Acquired **283** (6.9 g, 92%, > 95% pure on GCMS analysis) was directly used to the next reaction, analytical sample was purified by column chromatography (hexane - ethyl acetate 22:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.28 (m, 1H, H-5endo), 1.47 (m, 1H, H-6endo), 1.58 (dm, 1H, J_{gem} = 10.1, H-7a), 1.77 (tt, 1H, J_{gem} = $J_{5ex,6ex}$ = 12.6, $J_{5ex,4}$ = $J_{5ex,6en}$ = 4.5, H-5exo), 1.83 - 1.92 (m, 3H, H-2exo, H-6exo, H-7b), 1.96 (ddd, 1H, J_{gem} = 13.3, $J_{2en,3}$ = 7.5, $J_{2en,7a}$ = 2.7, H-2endo), 2.40 (dm, 1H, $J_{4,5ex}$ = 4.8, H-4), 3.64 (dm, 1H, $J_{3,2en}$ = 7.5, H-3), 3.70 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.01 (C-5), 32.11 (C-6), 39.13 (C-7), 40.74 (C-2), 42.80 (C-4), 51.61 (C-1), 51.78 (CH_3), 64.26 (C-3), 175.18 (COO). ESI MS *m/z* (%): 218.2 (100) [M+H]; HRMS ESI ($C_9H_{13}N_3O_2Na$) calculated: 218.09000, found: 218.08981. For $C_9H_{13}N_3O_2$ (195.22) calculated: 55.37% C, 6.71% H, 21.52% N; found: 55.32% C, 6.76% H, 21.30% N.

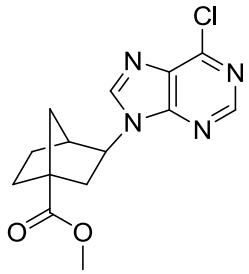


((1*R,3*S**,4*S**)-3-Aminobicyclo[2.2.1]heptan-1-yl)methanol (270)**

A solution of LAH (1M THF solution, 25 mL) was added dropwise to a stirred solution of **283** (2 g, 10 mmol) in dry THF (100 mL) under argon atmosphere at 0°C. After 2 hours at RT the reaction was quenched with carefull addition of water, solids were filtered off on a cellite pad and thoroughly washed with ethanol. Crude **270** was purified on Dowex 50 (H^+) and then precipitated as a hydrochloride (1.05 g, 59%) with 1M HCl - Et_2O solution from ethanolic solution (>94% pure on HPLC-MS analysis). Sample for analytical purposes was obtained by benzoylation of the crude amine and subsequent chromatography of tribenzoylated product on silica gel.

^{1}H NMR (500 MHz, DMSO): 1.24 (dm, 1H, J_{gem} = 9.3, H-7b), 1.38 - 1.47 (m, 2H, H-5endo, H-6exo), 1.55 (m, 1H, H-6endo), 1.72 (m, 1H, H-5exo), 1.98 (dm, 1H, J_{gem} = 9.3, H-7a), 2.02 (m, 1H, H-2endo), 2.06 (m, 1H, H-2exo), 2.61 (dm, 1H, $J_{4\text{-}5ex}$ = 4.4, H-4), 4.41 (m, 2H, CH_2-O), 4.58 (ddd, 1H, $J_{3\text{-}2en}$ = 8.2, $J_{3\text{-}2ex}$ = $J_{3\text{-}4}$ = 5.5, $J_{3\text{-}7}$ =

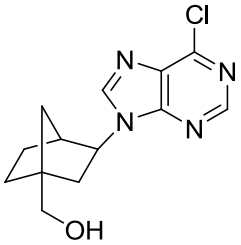
1.0, H-3), 7.23 (m, 4H, H-m), 7.32 - 7.37 (m, 6H, H-o, H-p), 7.49 (m, 2H, H-m'), 7.64 (tt, 1H, $J_{p'-m'}$ = 7.5, $J_{p'-o'}$ = 1.3, H-p'), 7.95 (m, 2H, H-o'). ^{13}C NMR (125.8 MHz, DMSO): 29.25 (C-5), 30.64 (C-6), 38.85 (C-7), 39.67 (C-2), 42.40 (C-4), 47.53 (C-1), 61.84 (C-3), 67.30 (CH_2-O), 128.60 (C-o), 128.65 (C-m), 128.92 (C-m'), 129.31 (C-o'), 129.93 (C-i'), 132.21 (C-p), 133.48 (C-p'), 137.49 (C-i), 165.79 (COO), 173.49 (CONH). ESI MS *m/z* (%): 454.2 (26) [M+H], 476.2 (100) [M+Na]; HRMS ESI ($C_{29}H_{27}NO_4Na$) calculated: 476.18378; found: 476.18371. For $C_{29}H_{27}NO_4$ (453.53) calculated: 76.80% C, 6.00% H, 3.09% N; found: 76.83% C, 6.08% H, 3.28% N.



Methyl (1*R,3*R**,4*R**)-3-(6-chloro-9*H*-purin-9-yl)bicyclo [2.2.1] heptane-1-carboxylate (284)**

A solution of DIAD (4.79 g, 23.7 mmol) in dry THF (40 mL) was added dropwise to a suspension of **281** (2.7 g, 15.8 mmol), triphenylphosphine (8.28 g, 31.6 mmol) and 6-chloropurine (3.66 g, 23.7 mmol) in dry THF (150 mL) under argon atmosphere. The reaction mixture was stirred at RT overnight and then refluxed for 5 hours, volatiles were evaporated and the residue was adsorbed on silica gel. Chromatography on silica gel (toluene - ethyl acetate 4:1) afforded **284** (3.7 g, 67%) as white crystals (m.p. = 149 - 150°C).

^{1}H NMR (500 MHz, $CDCl_3$): 1.62-1.69 (m, 2H, H-5endo,H-6endo), 1.79 (dm, 1H, J_{gem} = 10.6, H-7a), 1.91-2.06 (m, 3H, H-5exo, H-6exo, H-7b), 2.28 (dddd, 1H, J_{gem} = 13.9, J_{2ex-3} = 4.4, $J_{2ex-6ex}$ = 3.3, J_{2ex-4} = 0.8, H-2exo), 2.43 (ddd, 1H, J_{gem} = 13.9, J_{2en-3} = 8.5, J_{2en-7a} = 2.4, H-2endo), 2.72 (bd, 1H, J_{4-5ex} = 4.7, H-4), 3.71 (s, 3H, CH_3), 4.76 (ddd, 1H, J_{3-2en} = 8.5, J_{3-2ex} = 4.3, J_{3-7a} = 1.6, H-3), 8.26 (s, 1H, H-8'), 8.76 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, $CDCl_3$): 27.54 (C-5), 31.58 (C-6), 40.10 (C-7), 41.36 (C-2), 43.18 (C-4), 53.14 (C-1), 51.03 (CH_3), 58.64 (C-3), 131.95 (C-5'), 142.51 (C-8'), 151.08 (C-6'), 151.75 (C-4'), 151.78 (C-2'), 175.35 (COO). ESI MS m/z (%): 307.1 (85) [M+H], 329.1 (100) [M+Na]. For $C_{14}H_{15}O_2N_4Cl$ (306.75) calculated: 54.82% C, 4.93% H, 18.26% N; 10.43% Cl; found: 55.11% C, 5.08% H, 18.02% N, 10.36% Cl.

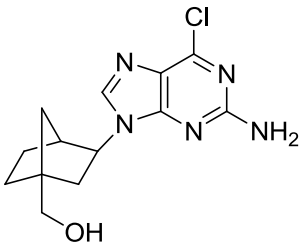


[(1*R,3*R**,4*R**)-3-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1] hept-1-yl]methanol (285)**

Method 1: DIBAL-H (1M, 26 mL) was added dropwise to a solution of **284** (2.64 g, 8.6 mmol) in dry dichlormethane (120 mL) at -78°C under argon atmosphere. The reaction mixture was stirred for 45 minutes and then carefully quenched with methanol (15 mL). Resulting slurry was filtered through a cellite pad, solid parts were washed with ethanol and product was purified by column chromatography on silica gel (ethyl acetate - toluene - acetone - ethanol 17:4:3:1). Crystallization from toluene-cyclohexane mixture afforded **285** (1.73 g, 72%) as white ctystals.

Method 2: 6-Chloropurine nucleobase was constructed according to method **A** (2 mmol of **270**, *n*-BuOH as a solvent, 160°C for 2h in MW reactor. Mobile phase 1-2% methanol in ethyl acetate. Crystallization from toluene - cyclohexane mixture. Yield 384 mg, 69% as white ctystals (m.p. = 150 - 151°C).

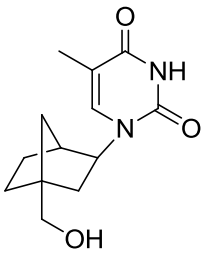
^{1}H NMR (500 MHz, DMSO): 1.38-1.44 (m, 2H, H-6endo,H-7a), 1.57-1.69 (m, 2H, H-5endo,H-6exo), 1.80 (dm, 1H, J_{gem} = 10.4, H-7b), 1.91 (m, 1H, H-5exo), 2.10 (dm, 1H, J_{gem} = 13.5, H-2exo), 2.16 (ddd, 1H, J_{gem} = 13.5, J_{2en-3} = 8.3, J_{2en-7a} = 1.4, H-2endo), 2.66 (bd, 1H, J_{4-5ex} = 4.7, H-4), 3.86 (m, 2H, CH_2O), 4.77 (ddd, 1H, J_{3-2en} = 8.3, J_{3-2ex} = 4.5, J_{3-7a} = 1.4, H-3), 8.28 (s, 1H, H-8'), 8.75 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 27.83 (C-5), 30.58 (C-6), 38.23 (C-7), 40.05 (C-2), 43.02 (C-4), 50.47 (C-1), 59.38 (C-3), 65.08 (CH_2O), 131.94 (C-5'), 142.92 (C-8'), 150.96 (C-6'), 151.65 (C-2'), 151.78 (C-4'). ESI MS *m/z* (%): 279.1 (100) [M+H]. For $C_{13}H_{15}N_4OCl$ (278.74) calculated: 56.02% C, 5.42% H, 20.10% N; 12.72% Cl; found: 56.29% C, 5.61% H, 19.85% N, 12.60% Cl.



[(1*R,3*R**,4*R**)-3-(2-Amino-6-chloro-9*H*-purin-9-yl) bicyclo[2.2.1]hept-1-yl]methanol (286)**

2-Amino-6-chloropurine nucleobase was constructed according to method **A** (2 mmol of **270**, water-EtOH mixture (1:1, *v/v*) as a solvent, 140°C for 1h in MW reactor). Mobile phase 1-5% methanol in ethyl acetate. Crystallization from toluene. Yield 486 mg, 83% as white ctystals (m.p. = 201°C).

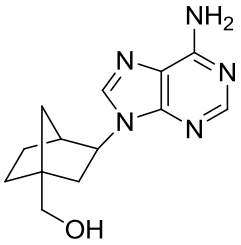
^{1}H NMR (500 MHz, DMSO): δ 1.19 - 1.26 (m, 2H, H-6endo, H-7b), 1.40 - 1.52 (m, 2H, H-5endo, H-6exo), 1.60 (dm, 1H, J_{gem} = 10.3, H-7a), 1.70 (m, 1H, H-5exo), 1.84 - 1.93 (m, 2H, H-2); 2.45 (m, 1H, H-4), 3.56 - 3.62 (m, 2H, CH_2O), 4.40 (m, 1H, H-3), 4.57 (t, 1H, J_{OH-CH2} = 5.3, OH), 6.89 (bs, 2H, NH_2), 8.23 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 27.73 (C-5), 30.43 (C-6), 37.99 (C-7), 42.45 (C-4), 50.44 (C-1), 58.06 (C-3), 63.61 (CH_2O), 123.85 (C-5'), 140.81 (C-8'), 149.47 (C-6'), 154.20 (C-4'), 159.78 (C-2'). ESI MS *m/z* (%): 294.1 (42) [M+H], 316.1 (100) [M+Na]; HRMS ESI ($C_{13}H_{17}N_5OCl$) calculated: 294.11161, found: 294.11170. For $C_{13}H_{16}ClN_5O$ (293.75) calculated: 53.15% C, 5.49% H, 12.07% Cl, 23.84 % N; found: 53.21% C, 5.59% H, 12.19% Cl, 23.60 % N.



1-[(1*R,2*R**,4*R**)-4-(Hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (287)**

Thymine nucleobase construction was performed according to method **E** starting from **270** (1.87 mmol). Mobile phase: 1-5% methanol in ethyl acetate. Crystallization from toluene - ethyl acetate mixture. Yield 326 mg, 69%, white crystals (m.p. =204°C).

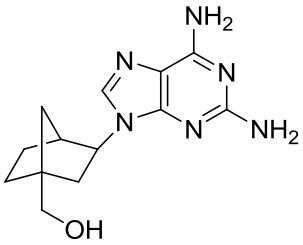
^{1}H NMR (500 MHz, DMSO): δ 1.13 - 1.19 (m, 2H, H-5endo, 7a), 1.34 - 1.51 (m, 4H, H-3exo, H-6endo, H-5exo, 7b), 1.65 (m, 1H, H-6exo), 1.78 (ddd, 1H, J_{gem} = 13.1, $J_{3en,2}$ = 8.3, $J_{3en,7a}$ = 2.4, H-3endo), 1.79 (d, 3H, $J_{CH3,6'}$ = 1.2, CH_3), 2.34 (bd, 1H, $J_{1,6ex}$ = 4.6, H-1), 3.52 (d, 2H, $J_{CH2,OH}$ = 5.4, CH_2O), 4.22 (bdd, 1H, $J_{2,3en}$ = 8.2, $J_{2,3ex}$ = 4.8, H-2), 4.54 (t, 1H, $J_{OH,CH2}$ = 5.4, OH), 7.48 (q, 1H, $J_{6',CH3}$ = 1.2, H-6'), 11.20 (bs, 1H, H-3'). ^{13}C NMR (125.8 MHz, DMSO): δ 12.38 (CH_3), 28.59 (C-6), 30.24 (C-5), 38.41 (C-7), 40.89 (C-1), 40.96 (C-3), 50.19 (C-4), 59.39 (C-2), 63.61 (CH_2O), 108.26 (C-5'), 137.19 (C-6'), 151.29 (C-2'), 163.91 (C-4'). ESI MS *m/z* (%): 273.1 (100) [M+H], 295.1 (56) [M+Na]; HRMS ESI ($C_{13}H_{18}N_2O_3Na$) calculated: 273.12096, found: 273.12098. For $C_{13}H_{18}N_2O_3$ (250.29) calculated: 62.38% C, 7.25% H, 11.19 % N; found: 62.12% C, 7.20% H, 11.37 % N.



[(1*R,3*R**,4*R**)-3-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1] hept-1-yl]methanol (288)**

Ammonolysis was performed according to method **F1** starting from **285** (140 mg, 0.5 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water-methanol mixture. Yield 100 mg, 77%, colorless crystals (m.p. = 199°C).

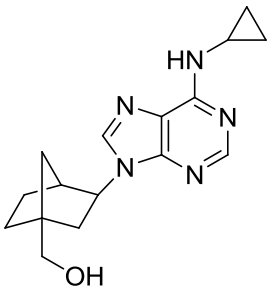
^{1}H NMR (500 MHz, DMSO): 1.20 (dm, 1H, J_{gem} = 10.2, H-7a), 1.24 (m, 1H, H-6endo), 1.46-1.52 (m, 2H, H-5endo,H-6exo), 1.63 (dm, 1H, J_{gem} = 10.2, H-7b), 1.70 (m, 1H, H-5exo), 1.91-1.94 (m, 2H, H-2), 2.45 (dm, 1H, $J_{4\text{-}5ex}$ = 4.6, H-4), 3.59 (m, 2H, CH_2O), 4.52 (m, 1H, H-3), 4.57 (t, 1H, $J_{OH\text{-}CH2}$ = 5.4, OH), 7.19 (bs, 2H, NH), 8.13 (s, 1H, H-2'), 8.22 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): 27.75 (C-5), 30.44 (C-6), 38.00 (C-7), 40.01 (C-2), 42.79 (C-4), 50.48 (C-1), 57.96 (C-3), 63.70 (CH_2O), 119.30 (C-5'), 138.41 (C-8'), 149.69 (C-4'), 152.43 (C-2'), 156.16 (C-6'). ESI MS *m/z* (%): 260 (100) [M+H], 282 (17) [M+Na]. For $C_{13}H_{17}ON_5$ (259.31) calculated: 60.21% C, 6.61% H, 27.01% N; found: 59.98% C, 6.67% H, 26.75% N.



[(1*R,3*R**,4*R**)-3-(2,6-diamino-9*H*-purin-9-yl)bicyclo [2.2.1]hept-1-yl]methanol (289)**

Ammonolysis was performed according to method **F2** starting from **286** (115 mg, 0.39 mmol). Mobile phase: 10-25% methanol in ethyl acetate. Crystallization from water. Yield 101 mg, 95%, light orange crystals (m.p. = 272°C).

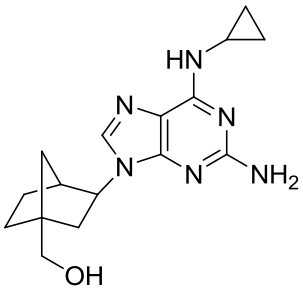
^{1}H NMR (500 MHz, DMSO): δ 1.17 (dm, 1H, J_{gem} = 10.2, H-7b), 1.22 (m, 1H, H-6endo), 1.36 - 1.50 (m, 2H, H-5endo, H-6exo), 1.62 (dm, 1H, J_{gem} = 10.2, H-7a), 1.68 (m, 1H, H-5exo), 1.82 - 1.88 (m, 2H, H-2), 2.36 (dm, 1H, $J_{4\text{-}5ex}$ = 4.7, H-4), 3.59 (d, 2H, $J_{CH2,OH}$ = 5.4, CH_2O), 4.33 (m, 1H, H-3), 4.57 (t, 1H, $J_{OH\text{-}CH2}$ = 5.7, OH), 5.74 (bs, 2H, 2'-NH_2), 6.63 (bs, 2H, 6'-NH_2), 7.78 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 27.81 (C-5), 30.52 (C-6), 37.93 (C-7), 40.00 (C-2), 42.75 (C-4), 50.34 (C-1), 57.13 (C-3), 63.70 (CH_2O), 113.67 (C-5'), 134.83 (C-8'), 151.97 (C-4'), 156.26 (C-6'), 160.28 (C-2'). ESI MS *m/z* (%): 275.3 (100) [M+H], 297.3 (18) [M+Na]; HRMS ESI ($C_{13}H_{19}ON_6$) calculated: 275.16149; found: 275.16144. For $C_{13}H_{18}N_6O$ (274.32) calculated: 56.92% C, 6.61% H, 30.64% N; found: 57.16% C, 6.59% H, 30.59% N.



{(1*R,3*R**,4*R**)-3-[6-(Cyclopropylamino)-9H-purin-9-yl] bicyclo[2.2.1]hept-1-yl}methanol (290)**

Nucleophilic displacement performed according to method **G1** starting from **285** (140 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 120 mg, 80 %, white crystals (m.p. = 146 – 146.5°C).

^{1}H NMR (500 MHz, DMSO): 0.60 and 0.71 (m, 4H, CH_2-cyklop), 1.20 (dm, 1H, J_{gem} = 10.1, H-7a), 1.25 (m, 1H, H-6endo), 1.46-1.53 (m, 2H, H-5endo,H-6exo), 1.63 (dm, 1H, J_{gem} = 10.2, H-7b), 1.70 (m, 1H, H-5exo), 1.91-1.94 (m, 2H, H-2), 2.45 (bd, 1H, $J_{4\text{-}5ex}$ = 4.7, H-4), 3.02 (bs, 1H, CH-cyklop), 3.59 (m, 2H, CH_2O), 4.54 (m, 1H, H-3), 4.57 (t, 1H, $J_{OH\text{-}CH2}$ = 5.4, OH), 7.85 (bs, 1H, NH), 8.22 (s, 2H, H-2', H-8'). ^{13}C NMR (125.8 MHz, DMSO): 6.58 (CH_2-cyklop), 27.75 (C-5), 30.45 (C-6), 38.00 (C-7), 40.03 (C-2), 42.78 (C-4), 50.48 (C-1), 57.96 (C-3), 63.70 (CH_2O), 119.70 (C-5'), 138.25 (C-8'), 149.04 (C-4'), 152.34 (C-2'), 155.73 (C-6'). ESI MS *m/z* (%): 300 (100) [M+H], 322 (41) [M+Na]. For $C_{16}H_{21}ON_5$ (299.37) calculated: 64.19% C, 7.07% H, 23.39% N; found: 63.98% C, 7.21% H, 23.31% N.

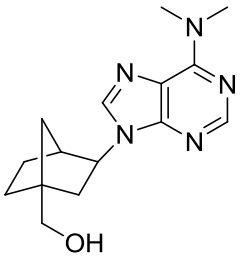


(1*R,2*R**,4*R**)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.1]heptan-2-ol (291)**

Nucleophilic displacement performed according to method **G2** starting from **286** (500 mg, 1.53 mmol). Mobile phase: 5-15% methanol in ethyl acetate. Crystallization from water. Yield 400 mg, 83 %, white crystals (m.p. = 134°C).

^{1}H NMR (500 MHz, DMSO): δ 0.57 and 0.64 (m, 4H, CH_2-cyclop), 1.17 (m, 1H, H-7b), 1.22 (m, 1H, H-6endo), 1.39 - 1.50 (m, 2H, H-5endo, H-6exo), 1.61 (dm, 1H, J_{gem} = 10.1, H-7a), 1.68 (m, 1H, H-5exo), 1.81 - 1.88 (m, 2H, H-2), 2.35 (dm, 1H, $J_{4\text{-}5ex}$ = 4.9, H-4), 3.03 (bs, 1H, CH-cyclop), 3.58 (d, 2H, $J_{CH2,OH}$ = 5.4, CH_2O), 4.34 (m, 1H, H-3), 4.56 (t, 1H, $J_{OH,CH2}$ = 5.4, OH), 5.79 (bs, 2H, NH_2), 7.24 (bs, 1H, NH), 7.77 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.58 (CH_2-cyclop), 27.81 (C-5), 30.52 (C-6), 37.93 (C-7), 40.03 (C-2), 42.75 (C-4), 50.34 (C-1), 57.08 (C-3), 63.70 (CH_2O), 113.92 (C-5'), 134.54 (C-8'), 151.5 (C-4'), 156.03 (C-6'), 160.19 (C-2'). ESI MS *m/z* (%): 315.3 (100) [M+H], 337.3 (11) [M+Na]; HRMS ESI

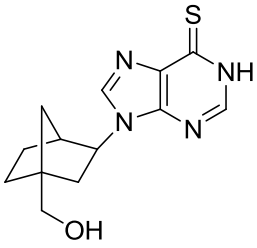
($C_{16}H_{23}ON_6$) calculated: 315.19279; found: 315.19276. For $C_{16}H_{22}N_6O$ (314.39) calculated: 61.13% C, 7.05% H, 26.73% N; found: 61.29% C, 7.12% H, 26.59% N.



{(1*R,3*R**,4*R**)-3-[6-(Dimethylamino)-9H-purin-9-yl]bicyclo [2.2.1]hept-1-yl}methanol (292)**

Nucleophilic displacement performed according to method **H1** starting from **285** (140 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 100 mg, 69 %, white crystals (m.p. = 120 - 121°C).

^{1}H NMR (500 MHz, DMSO): 1.21 (dm, 1H, J_{gem} = 10.2, H-7a), 1.25 (m, 1H, H-6en), 1.45-1.53 (m, 2H, H-5endo, H-6exo), 1.60 (dm, 1H, J_{gem} = 10.2, H-7b), 1.70 (m, 1H, H-5exo), 1.87 (dm, 1H, J_{gem} = 13.2, H-2exo), 1.94 (ddd, 1H, J_{gem} = 13.2, J_{2en-3} = 8.4, J_{2en-7a} = 2.3, H-2endo), 2.44 (bd, 1H, J_{4-5ex} = 4.7, (H-4), 3.45 (bs, 6H, N-CH_3), 3.59 (m, 2H, CH_2O), 4.54 (ddd, 1H, J_{3-2en} = 8.5, J_{3-2ex} = 4.6, J_{3-7a} = 1.2, H-3), 4.57 (t, 1H, J_{OH-CH2} = 5.3, OH), 8.20 (s, 1H, H-2'), 8.23 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): 27.77 (C-5), 30.42 (C-6), 38.02 (C-7), 38.45 (N-CH_3), 40.11 (C-2), 42.67 (C-4), 50.50 (C-1), 57.91 (C-3), 63.71 (CH_2O), 119.86 (C-5'), 137.21 (C-8'), 150.45 (C-4'), 151.79 (C-2'), 154.43 (C-6'). ESI MS *m/z* (%): 288 (100) [M+H], 310 (44) [M+Na]. For $C_{15}H_{21}ON_5$ (287.36) calculated: 62.70% C, 7.37% H, 24.37% N; found: 62.60% C, 7.32% H, 24.25% N.

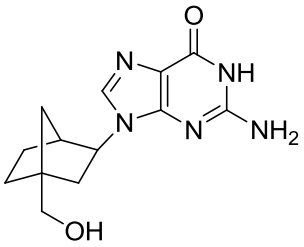


[(1*R,3*R**,4*R**)-3-(6-Thio-9H-purin-9-yl)bicyclo[2.2.1] hept-1-yl]methanol (293)**

Nucleophilic displacement performed according to method **I** starting from **285** (140 mg, 0.5 mmol). Yield 94 mg, 68%, white powder (m.p. > 320°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): 1.20-1.27 (m, 2H, H-6endo, H-7a), 1.45-1.53 (m, 2H, H-5endo, H-6exo), 1.59 (dm, 1H, J_{gem} = 10.3, H-7b), 1.70 (m, 1H, H-5exo), 1.87-1.97 (m, 2H, H-2), 2.47 (bd, 1H, J_{4-5ex} = 4.6, H-4), 3.59 (m, 2H, CH_2O), 4.53 (ddd, 1H, J_{3-2en} = 8.4, J_{3-2ex} = 4.7, J_{3-7a} = 1.3, H-3), 4.56 (bs, 1H, OH), 8.18 (d, 1H, $J_{2'-SH}$ = 3.8, H-2'), 8.39 (s, 1H, H-8'), 13.70 (bs, 1H, SH). ^{13}C NMR (125.8 MHz, DMSO): 27.65 (C-5), 30.35 (C-6), 37.96 (C-7), 40.00 (C-2), 42.78 (C-4), 50.53 (C-1), 58.57 (C-3), 63.60 (CH_2O), 135.53 (C-5'), 140.65 (C-8'), 144.19 (C-4'), 144.83

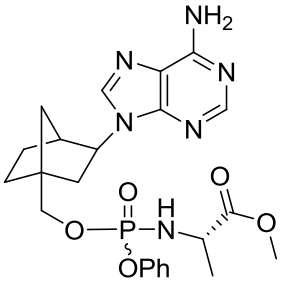
(C-2'), 176.01 (C-6'). ESI MS *m/z* (%): 277 (6) [M+H], 299 (31) [M+Na]. For $C_{13}H_{16}ON_4S$ (276.36) calculated: 56.50% C, 5.84% H, 20.27% N; 11.60% S; found: 56.28% C, 5.85% H, 20.04% N, 11.65% S.



2-amino-9-[(1*R,2*R**,4*R**)-4-(hydroxymethyl)bicyclo [2.2.1]hept-2-yl]-1,9-dihydro-6*H*-purin-6-one (294)**

Hydrolysis to guanine derivative was performed according to method **J** starting from **286** (100 mg, 0.53 mmol). Yield 56 mg, 60%, pale orange powder (m.p. > 335°C (decomp)).

^{1}H NMR (500 MHz, DMSO): δ 1.17 (dm, 1H, J_{gem} = 10.2, H-7b), 1.21 (m, 1H, H-5endo), 1.37 - 1.49 (m, 2H, H-6endo, H-5exo), 1.58 (dm, 1H, J_{gem} = 10.2, H-7a), 1.67 (m, 1H, H-6exo), 1.78 - 1.87 (m, 2H, H-3), 2.35 (dm, 1H, $J_{1\text{-}6ex}$ = 4.7, H-1), 3.54 - 3.60 (m, 2H, CH_2O), 4.29 (m, 1H, H-2), 4.56 (t, 1H, $J_{OH\text{-}CH2}$ = 5.3, OH), 6.47 (bs, 2H, NH_2), 7.77 (s, 1H, H-8'), 10.58 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 27.80 (C-6), 30.47 (C-5), 37.86 (C-7), 42.77 (C-1), 50.38 (C-4), 57.48 (C-2), 63.64 (CH_2O), 117.00 (C-5'), 134.78 (C-8'), 151.25 (C-4'), 153.55 (C-2'), 157.02 (C-6'). ESI MS *m/z* (%): 276.2 (15) [M+H], 298.2 (100) [M+Na]; HRMS ESI ($C_{13}H_{18}O_2N_5$) calculated: 276.14550, found: 244.14557. For $C_{13}H_{17}N_5O_2$ (275.31) calculated: 56.71% C, 6.22% H, 25.44% N; found: 56.93% C, 6.11% H, 25.20% N.

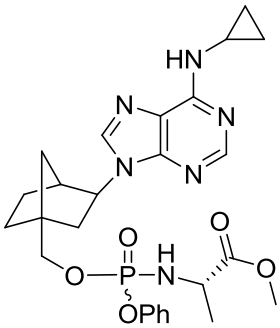


Methyl (2S)-2-{[({(1*R,3*R**,4*R**)3-[6-amino-9H-purin-9-yl] bicyclo[2.2.1]heptan-1-yl}methoxy)(phenoxy) phosphoryl]amino}propanoate (295)**

Phosphoramidate was prepared according to method **L** starting from **288** (105 mg, 0.41 mmol). Mobile phase: 5-15% methanol in ethyl acetate. Yield 120 mg, 59%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, DMSO): δ 1.22 - 1.24 (m, 3H, CH-*CH*$_3$), 1.25 - 1.36 (m, 2H, H-6ex, H-7b), 1.48 - 1.55 (m, 2H, H-5en, H-6en), 1.64 - 1.73 (m, 2H, H-5ex, H-7a), 1.88 - 2.05 (m, 2H, H-2en, H-2ex), 2.48 (m, 1H, H-4), 3.58 and 3.59 (m, 3H, O-CH_3), 3.85 (m, 1H, NH-*CH*), 4.16 - 4.25 (m, 2H, 1-CH_2-O), 4.54 (m, 1H, H-3), 5.98 (m, 1H, NH), 7.11 - 7.21 (m, 5H, NH_2, H-2'', H-4''), 7.33 (m, 2H, H-3''), 8.13 (m, 1H, H-2'), 8.23 - 8.25 (m, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 19.81 and

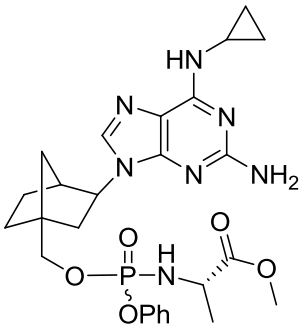
19.86 (d, $J_{CH3,P}$ = 7.3, CH-*CH*$_3$), 27.51 and 27.52 (C-5), 30.07 - 30.21 (m, C-6), 37.90 and 37.95 (C-7), 39.5 (C-2), 42.75 - 42.81 (m, C-4), 48.46 and 48.52 (d, J_{1-P} = 8.2, C-1), 49.88 and 50.02 (NH-*CH*), 52.00 and 52.02 (O-*CH*$_3$), 57.61 - 57.71 (C-3), 68.59 and 68.74 (m, 1-CH_2-O), 119.33 (C-5'), 120.44 and 120.45 (d, $J_{2'',P}$ = 4.5, C-2''), 124.63 (C-4''), 129.67 and 129.72 (C-3''), 138.42 and 138.46 (C-8'), 149.67 (C-4'), 151.01 (dm, $J_{1'',P}$ = 6.7, C-1''), 152.43 (C-2'), 156.16 (C-6'), 173.89 and 173.93 (COO). ESI MS *m/z* (%): 501.2 (100) [M+H], 523.2 (60) [M+Na]; HRMS ESI ($C_{23}H_{30}O_5N_6P$) calculated: 501.20098; found: 501.20091.



Methyl (2S)-2-{[({(1*R,3*R**,4*R**)3-[6-(cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]heptan-1-yl}methoxy)(phenoxy)phosphoryl]amino}propanoate (296)**

Phosphoramidate was prepared according to method **L** starting from **290** (200 mg, 0.67 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Yield 136 mg, 38%, white foam.

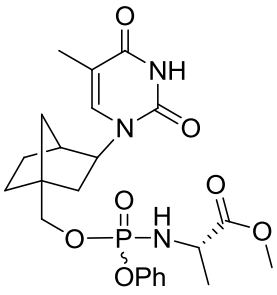
^{1}H NMR (500 MHz, DMSO): 0.61 and 0.71 (m, 4H, CH_2-cyclop), 1.20 – 1.37 (m, 5H, CH-**CH$_3$**, H-6endo, H-7a), 1.46 – 1.57 (m, 2H, H-5endo, H-6exo), 1.63 – 1.75 (m, 2H, H-5exo, H-7b), 1.88 – 2.06 (m, 2H, H-2), 2.48 (m, 1H, H-4), 3.04 (bs, 1H, CH-cyclop), 3.57 and 3.59 (s, 3H, OCH_3), 3.84 (m, 1H, CH-COO), 4.16 – 4.24 (m, 2H, CH_2-O), 4.56 (m, 1H, H-3), 5.98 (m, 1H, P-NH), 7.11 - 7.20 (m, 3H, H-2'', H-4''), 7.33 (m, 2H, H-3''), 7.87 (bs, 1H, 6'-NH), 8.22 - 8.25 (m, 2H, H-2', H-8'). ^{13}C NMR (125.8 MHz, DMSO): 6.57 (CH_2-cyclop), 19.85 (CH-CH_3), 27.52 (C-5), 30.08 and 30.22 (C-6), 37.90 and 37.95 (C-7), 39.60 (C-2), 42.77 (C-4), 48.51 (C-1), 49.88 and 52.03 (CH-COO), 52.03 (OCH_3), 57.62 and 57.66 (C-3), 68.65 (CH_2O), 119.71 (C-5'), 120.45 and 120.47 (C-2''), 124.65 (C-4''), 129.72 (C-3''), 138.28 (C-8'), 149.00 (C-4'), 151.00 and 151.04 (C-1''), 152.35 (C-2'), 155.71 (C-6'), 173.92 and 173.94 (COO). HRMS ESI ($C_{26}H_{34}N_6O_5P$) calculated: 541.2323, found: 541.2322.



Methyl (2S)-2-{[({(1*R,3*R**,4*R**)3-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]heptan-1-yl}methoxy)(phenoxy)phosphoryl]amino}propanoate (297)**

Phosphoramidate was prepared according to method **L** starting from **291** (307 mg, 0.98 mmol). Mobile phase: 5-20% methanol in ethyl acetate. Yield 300 mg, 55%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, DMSO): δ 0.56 - 0.67 (m, 4H, CH_2-cyclop), 1.21 - 1.32 (m, 5H, CH-*CH_3*, H-6ex, H-7b), 1.41 - 1.55 (m, 2H, H-5en, H-6en), 1.61 - 1.73 (m, 2H, H-5ex, H-7a), 1.81 - 1.98 (m, 2H, H-2en, H-2ex), 2.38 (m, 1H, H-4), 3.03 (bs, 1H, CH-cyclop), 3.58 - 3.59 (m, 3H, O-CH_3), 3.85 (m, 1H, NH-*CH*), 4.16 - 4.24 (m, 2H, 1-CH_2-O), 4.36 (m, 1H, H-3), 5.81 (bs, 1H, NH_2), 5.97 (m, 1H, NH), 7.13 - 7.21 (m, 3H, H-2'', H-4''), 7.27 (bs, 1H, NH-cyclop), 7.34 (m, 2H, H-3''), 7.79 - 7.80 (m, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.59 (CH_2-cyclop), 19.82 and 19.87 (d, $J_{CH3,P}$ = 7.5, CH-*CH_3*), 23.9 (CH-cyclop), 27.61 (C-5), 30.17 - 30.31 (m, C-6), 37.84 and 37.89 (C-7), 39.8 (C-2), 42.79 and 42.81 (C-4), 48.36 and 48.40 (d, J_{1-P} = 8.2, C-1), 49.88 and 50.03 (NH-*CH*), 52.02 and 52.04 (O-*CH_3*), 56.78 - 56.85 (m, C-3), 68.66 and 68.80 (m, 1-CH_2-O), 113.93 (C-5'), 120.43 and 120.45 (d, $J_{2'',P}$ = 4.7, C-2''), 124.64 (C-4''), 129.71 and 129.73 (C-3''), 134.62 (C-8'), 150.97 - 151.07 (m, C-4', C-1''), 156.05 (C-6'), 160.21 (C-2'), 173.91 and 173.94 (COO). ESI MS *m/z* (%): 556.3 (100) [M+H], 578.3 (35) [M+Na]; HRMS ESI ($C_{26}H_{35}O_5N_7P$) calculated: 556.24318; found: 556.24292.



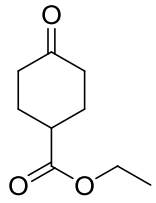
Methyl (2S)-2-[({[(1*R,3*R**,4*R**)-3-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)bicyclo[2.2.1]heptan-1-yl]methoxy}(phenoxy)phosphoryl)amino]propanoate (298)**

Phosphoramidate was prepared according to method **L** starting from **287** (326 mg, 1.3 mmol). Mobile phase: 1-5% methanol in ethyl acetate. Yield 185 mg, 29%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, DMSO): δ 1.21 - 1.26 (m, 5H, H-6b, 7b, NH-CH-*CH_3*), 1.35 - 1.54 (m, 4H, H-2b, H-5b, H-6a, 7a), 1.66 (m, 1H, H-5a), 1.79 (m, 3H, 5'-*CH_3*), 1.86 (m, 1H, H-2a), 2.39 (m, 1H, H-4), 3.58 and 3.59 and 3.60 and 3.60 (s, 3H, O-

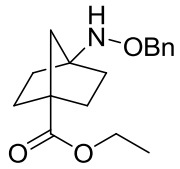
CH_3), 3.83 (m, 1H, NH-*CH*), 4.10 - 4.17 (m, 2H, 1-CH_2-O), 4.22 (m, 1H, H-3), 5.96 (m, 1H, NH), 7.13 - 7.19 (m, 3H, H-2'', H-4''), 7.32 - 7.37 (m, 2H, H-3''), 7.50 (m, 1H, H-6'), 11.22 (bs, 1H, H-3'). ^{13}C NMR (125.8 MHz, DMSO): δ 12.35 (5'-CH_3), 19.76 - 19.88 (m, NH-CH-*CH_3*), 28.29 - 28.36 (m, C-5), 29.88 - 30.06 (m, C-6), 38.30 and 38.35 (C-7), 40.31 (C-4), 40.77 (C-2), 48.23 (C-1), 49.88 and 50.02 (NH-*CH*), 52.00 (O-*CH_3*), 59.17 (C-3), 68.44 - 68.71 (m, 1-CH_2), 108.31 and 108.33 (C-5), 120.43 and 120.47 (C-2''), 124.63 (C-4''), 126.66 - 129.71 (C-3''), 137.16 (C-6'), 150.98 and 151.04 (C-2'), 151.27 and 151.28 (C-1''), 163.93 (C-4'), 173.87 and 173.91 (COO). ESI MS *m/z* (%): 492.4 (3) [M+H], 514.3 (100) [M+Na]; HRMS ESI ($C_{23}H_{30}O_7N_3NaP$) calculated: 514.17136; found: 514.17144. For $C_{23}H_{30}N_3O_7P$ (491.47) calculated: 56.21% C, 6.15% H, 8.55% N; 6.30% P; found: 56.04% C, 6.20% H, 8.14% N, 5.95% P.

5.6. Carbocyclic nucleoside analogues locked in East conformation



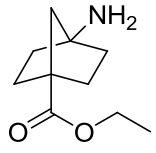
Ethyl 4-oxocyclohexanecarboxylate (308)

To a suspension of PDC (15 g, 40 mmol) and crushed molecular sieves (15 g) in DCM (200 mL) was added a solution of **307**[148] (5 g, 29 mmol) in DCM (20 mL) and the reaction mixture was vigorously stirred at RT for 24 h. Solid parts were filtered off on a cellite pad, volatiles were evaporated and the dark-brown slurry was filtered through a plug of silica gel in toluene - ethyl acetate mixture (4:1) to afford **308** (4,8 g, >94% pure on GC-MS analysis) of as a clear oil. Further purification by distilation under reduced pressure (140 °C, 5 mbar) afforded pure **308** (4.3 g, 86%). Spectral characteristics match those described in literature.[148]



Ethyl 4-[(benzyloxy)amino]bicyclo[2.2.1]heptane-1-carboxylate (313)

To a refluxing solution of **312**[132] (10.73 g, 29.1 mmol) and Bu_3SnH (23.5 mL, 87.4 mmol) in dry and deoxygenated toluene (300 mL) was added AIBN (300 mg) in one portion. After another 2 hours of reflux additional Bu_3SnH (16 mL, 58.2 mmol) and AIBN (300 mg) and after further 3 hours of reflux the reaction mixture was cooled, quenched with methyliodide (5 mL), volatiles were evaporated and column chromatography of the residue (hexane - ethyl acetate 23:2) afforded **313** (4.1 g, 49%) as a clear oil. Spectral characteristics match those described in literature.[132]

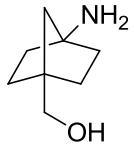


Ethyl 4-aminobicyclo[2.2.1]heptane-1-carboxylate (314)

To a solution of **313** (3.5g, 12.1 mmol) in dry methanol (50 mL) was added $Pd(OH)_2/C$ (600 mg) and the reaction mixture was treated with hydrogen (60 atm) for 24h. Catalyst was filtered off on a cellite pad and volatiles were evaporated. Purification of the product was performed on Dowex 50 (H^+) and afforded **314 (**1.9 g, 85 %) as a brownish gel.

^{1}H NMR (500 MHz, DMSO): 1.16 (t, 3H, $J_{CH3-CH2}$ = 7.1, CH_3), 1.40 (m, 2H, H-3exo, H-5exo), 1.46 (m, 2H, H-7), 1.51 – 1.58 (m, 4H, H-2endo, H-6endo, H-3endo, H-5endo), 1.89 (m, 2H, H-2exo, H-6exo), 4.03 (q, 2H, $J_{CH2-CH3}$ = 7.1, CH_2O). ^{13}C NMR (125.8 MHz, DMSO): 14.33 (CH_3), 33.10 (C-2, C-6), 36.45 (C-3, C-5), 48.97

(C-7), 50.47 (C-1), 59.78 (CH_2O), 62.86 (C-4), 175.10 (COO). HRMS ($C_{10}H_{17}NO_2$) calculated: 184.1338, found: 184.1332 (M+H).

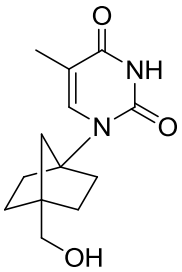


(4-Aminobicyclo[2.2.1]hept-1-yl)methanol (315)

Method 1: To a solution of **314** (250 mg, 1.4 mmol) in dry THF (15 mL) was added $LiAlH_4$ (210 mg, 5.5 mmol) and the mixture was heated to reflux for 5h. After cooling to RT, reaction was quenched by careful addition of water, filtered through a pad of cellite and the solid parts were thoroughly washed with ethanol. Purification was performed on Dowex 50 (H^+) affording **315** (130 mg, 67 %) as a brownish gel which solidifies on standing.

Method 2: To a solution of **313** (1.6 g, 5.5 mmol) in dry diglyme (40 mL) was added BH_3-THF complex (1M solution in THF, 20 mL) and the mixture was heated in a pressure vessel on 110°C for 48h. After cooling to RT, reaction was quenched by careful addition of water and solvents were evaporated. The residue was suspended in ethanol (150 mL), solid parts were filtered off on a cellite pad and thoroughly washed with ethanol. Crude product was purified on Dowex 50 (H^+) to afford **315** (750 mg, 95 %) as clear oil which crystallizes on standing. Sample for analytical purposes was obtained by acetylation of crude amine and subsequent chromatography of diacetylated product on silica gel. Mobile phase: toluene - ethyl acetate 1:1.

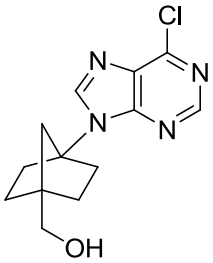
^{1}H NMR (500 MHz, DMSO): 1.32 (m, 2H, H-2endo, H-6endo), 1.53 – 1.65 (m, 6H, H-2exo, H-6exo, H-3endo, H-5endo, H-7), 1.76 (s, 3H, NH-CO-**CH_3**), 1.82 (m, 2H, H-3exo, H-5exo), 2.01 (s, 3H, O-CO-**CH_3**), 4.03 (s, 2H, CH_2O), 7.91 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): 20.84 (O-CO-**CH_3**), 23.39 (NH-CO-**CH_3**), 31.54 (C-2, C-6), 33.66 (C-3, C-5), 43.60 (C-7), 45.28 (C-1), 61.43 (C-4), 67.22 (CH_2O), 169.33 (NH-**CO**), 170.58 (O-**CO**). ESI MS *m/z* (%): 226.2 (17) [M+H], 248.1 (100) [M+Na]. For $C_{12}H_{19}NO_3$ (225.28) calculated: 63.98% C, 8.50% H, 6.22% N; found: 63.96% C, 8.68% H, 6.16% N.



1-[4-(Hydroxymethyl)bicyclo[2.2.1]hept-1-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (316)

Thymine nucleobase construction was performed according to method **E** starting from **315** (141 mg, 1 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - ethyl acetate mixture. Yield 177 mg, 71%, colorless needles (m.p. = 200-201°C).

^{1}H NMR (500 MHz, DMSO): 1.33 (m, 2H, H-3'endo, H-5'endo), 1.62 - 1.71 (m, 4H, H-2'exo, H-6'exo, H-3'exo, H-5'exo), 1.75 (d, 3H, J_{CH3-6} = 1.2, CH_3), 1.81 (bs, 2H, H-7'), 2.30 (m, 2H, H-2'endo, H-6'endo), 3.43 (d, 2H, J_{CH2-OH} = 5.2, CH_2O), 4.58 (t, 1H, J_{OH-CH2} = 5.3, OH), 7.45 (q, 1H, J_{6-CH3} = 1.2, H-6), 11.06 (bs, 1H, H-3). ^{13}C NMR (125.8 MHz, DMSO): 12.21 (CH_3), 31.28 (C-3', C-5'), 33.47 (C-2', C-6'), 44.22 (C-7'), 46.98 (C-4'), 64.49 (CH_2O), 69.95 (C-1'), 107.72 (C-5), 139.97 (C-6), 150.97 (C-2), 164.30 (C-4). ESI MS *m/z* (%): 251.2 (50) [M+H], 273.2 (100) [M+Na]. For $C_{13}H_{18}N_2O_3$ (250.29) calculated: 62.38% C, 7.25% H, 11.19% N; found: 62.05% C, 7.10% H, 10.98% N.



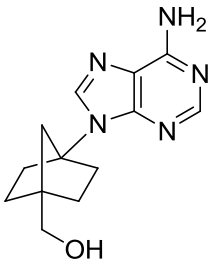
[4-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]hept-1-yl]methanol (317)

Method 1: 6-Chloropurine nucleobase was constructed according to method **C2** (140 mg, 1 mmol of **315**, *n*-BuOH as a solvent, 160°C for 4h in MW reactor. Mobile phase: toluene - ethyl acetate 2:1 and toluene - ethyl acetate 6:1. Crystallization from toluene - cyclohexane mixture. Yield 170 mg, 61% as white ctystals (m.p. = 176.5-178°C).

Method 2: 6-Chloropurine nucleobase was constructed according to method **A** (282 mg, 2 mmol of **315**, *n*-BuOH as a solvent, 160°C for 2h in MW reactor. Mobile phase 1-2% methanol in ethyl acetate. Yield 335 mg, 60% as white ctystals.

^{1}H NMR (500 MHz, DMSO): 1.46 (m, 2H, H-2endo, H-6endo), 1.81 (m, 2H, H-2exo, H-6exo), 2.10 (m, 2H, H-3exo, H-5exo), 2.13 (bs, 2H, H-7), 2.28 (m, 2H, H-3endo, H-5endo), 3.51 (d, 2H, J_{CH2-OH} = 5.3, CH_2O), 4.68 (t, 1H, J_{OH-CH2} = 5.3, OH), 8.68 (s, 1H, H-8'), 8.77 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 31.29 (C-2, C-6), 34.55 (C-3, C-5), 43.57 (C-7), 48.51 (C-1), 64.20 (CH_2O), 66.22 (C-4), 131.72 (C-5'), 146.54 (C-8'), 149.37 (C-6'), 151.24 (C-2'), 152.35 (C-4'). ESI MS *m/z* (%): 279.1 (100) [M+H], 301.1 (86) [M+Na]. For $C_{13}H_{15}N_4OCl$ x 1/5 C_7H_8 (297.17)

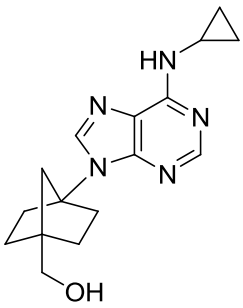
calculated: 58.20% C, 5.63% H, 18.85% N, 11.93% Cl; found: 57.96% C, 5.63% H, 18.73% N, 11.73%.



[4-(6-amino-9H-purin-9-yl)bicyclo[2.2.1]hept-1-yl]methanol (318)

Ammonolysis was performed according to method **F1** starting from **317** (150 mg, 0.53 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water-methanol mixture. Yield 128 mg, 91%, colorless needles (m.p. = 225°C)

^{1}H NMR (500 MHz, DMSO): 1.43 (m, 2H, H-2endo, H-6endo), 1.78 (m, 2H, H-2exo, H-6exo), 2.06 (bs, 2H, H-7), 2.07 (m, 2H, H-3exo, H-5exo), 2.20 (m, 2H, H-3endo, H-5endo), 3.50 (d, 2H, $J_{CH2\text{-}OH}$ = 5.3, CH_2O), 4.62 (t, 1H, $J_{OH\text{-}CH2}$ = 5.3, OH), 7.15 (bs, 2H, NH_2), 8.07 (s, 1H, H-8'), 8.11 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 31.38 (C-2, C-6), 34.60 (C-3, C-5), 43.61 (C-7), 48.48 (C-1), 64.39 (CH_2O), 65.37 (C-4), 119.81 (C-5'), 139.59 (C-8'), 150.11 (C-4'), 152.17 (C-2'), 156.29 (C-6'). ESI MS *m/z* (%): 260.2 (100) [M+H], 282.2 (32) [M+Na]. For $C_{13}H_{17}N_5O$ (259.31) calculated: 60.21% C, 6.61% H, 27.01% N; found: 59.92% C, 6.60% H, 26.80% N.

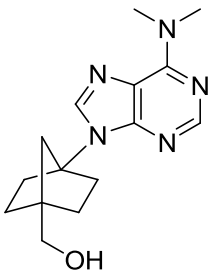


{4-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-1-yl}methanol (319)

Nucleophilic displacement performed according to method **G1** starting from **317** (150 mg, 1.53 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene-cyclohexane mixture. Yield 146 mg, 91 %, white crystals (m.p. = 157-158°C).

^{1}H NMR (500 MHz, DMSO): 0.60 and 0.71 (m, 4H, CH_2-cyclop), 1.43 (m, 2H, H-2endo, H-6endo), 1.78 (m, 2H, H-2exo, H-6exo), 2.06 (bs, 2H, H-7), 2.07 (m, 2H, H-3exo, H-5exo), 2.20 (m, 2H, H-3endo, H-5endo), 3.02 (bs, 1H, CH-cyclop), 3.50 (d, 2H, $J_{CH2\text{-}OH}$ = 5.3, CH_2O), 4.62 (t, 1H, $J_{OH\text{-}CH2}$ = 5.3, OH), 7.81 (bs, 1H, NH), 8.07 (s, 1H, H-8'), 8.22 (bs, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 6.54 (CH_2-cyclop), 31.38 (C-2, C-6), 34.61 (C-3, C-5), 43.63 (C-7), 48.47 (C-1), 64.38 (CH_2O), 65.39 (C-4), 120.18 (C-5'), 139.42 (C-8'), 149.7 (C-4'), 152.07 (C-2'), 155.83 (C-

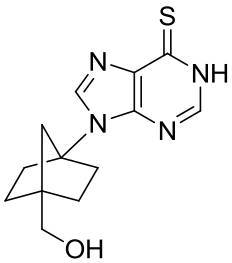
6'). ESI MS *m/z* (%): 300.2 (100) [M+H], 322.2 (3) [M+Na]. For $C_{16}H_{21}N_5O$ (299.37) calculated: 64.19% C, 7.07% H, 23.39% N; found: 64.11% C, 7.02% H, 23.40% N.



{4-[6-(Dimethylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-1-yl}methanol (320)

Nucleophilic displacement performed according to method **H2** starting from **317** (150 mg, 0.53 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - ethyl acetate mixture. Yield 135 mg, 87 %, colorless crystals (m.p. = 155°C).

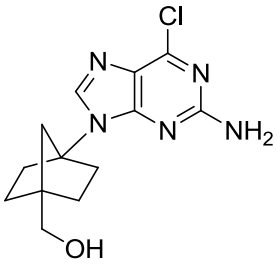
^{1}H NMR (500 MHz, DMSO): 1.43 (m, 2H, H-2endo, H-6endo), 1.78 (m, 2H, H-2exo, H-6exo), 2.04 (m, 2H, H-3exo, H-5exo), 2.06 (bs, 2H, H-7), 2.22 (m, 2H, H-3endo, H-5endo), 3.44 (bs, 6H, CH_3), 3.50 (d, 2H, $J_{CH2\text{-}OH}$ = 5.3, CH_2O), 4.63 (t, 1H, $J_{OH\text{-}CH2}$ = 5.3, OH), 8.08 (s, 1H, H-8'), 8.19 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 31.37 (C-2, C-6), 34.50 (C-3, C-5), 37.97 (CH_3), 43.60 (C-7), 48.42 (C-1), 64.38 (CH_2O), 65.42 (C-4), 120.36 (C-5'), 138.47 (C-8'), 150.95 (C-4'), 151.48 (C-2'), 154.54 (C-6'). ESI MS *m/z* (%): 288.2 (100) [M+H]. For $C_{15}H_{21}N_5O$ (287.36) calculated: 62.70% C, 7.37% H, 24.37% N; found: 62.43% C, 7.44% H, 24.00% N.



[4-(6-sulfanyl-9H-purin-9-yl)bicyclo[2.2.1]hept-1-yl] methanol (321)

Nucleophilic displacement performed according to method **I** starting from **317** (150 mg, 0.53 mmol). Yield 121 mg, 81%, white powder (m.p. > 320°C (decomp.)).

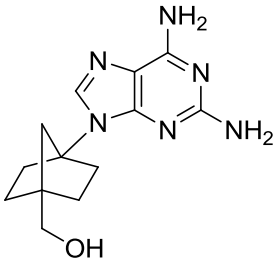
^{1}H NMR (500 MHz, DMSO): 1.43 (m, 2H, H-2endo, H-6endo), 1.78 (m, 2H, H-2exo, H-6exo), 2.04 (m, 2H, H-3exo, H-5exo), 2.06 (bs, 2H, H-7), 2.21 (m, 2H, H-3endo, H-5endo), 3.49 (s, 2H, CH_2O), 4.64 (bs, 1H, OH), 8.17 (d, 1H, $J_{2'\text{-}SH}$ = 3.9, H-2'), 8.25 (s, 1H, H-8'), 13.71 (bs, 1H, SH). ^{13}C NMR (125.8 MHz, DMSO): 31.31 (C-2, C-6), 34.78 (C-3, C-5), 43.68 (C-7), 48.48 (C-1), 64.23 (CH_2O), 65.89 (C-4), 136.00 (C-5'), 142.02 (C-8'), 144.35 (C-2'), 144.35 (C-4'), 176.05 (C-6'). ESI MS *m/z* (%): 277.2 (60) [M+H], 299.2 (100) [M+Na]. For $C_{13}H_{16}N_4OS$ (276.36) calculated: 56.50% C, 5.84% H, 20.27% N, 11.60% S; found: 56.17% C, 5.77% H, 20.15% N, 11.15% S.



[4-(2-Amino-6-chloro-9*H*-purin-9-yl)bicyclo[2.2.1]hept-1-yl]methanol (322)

2-Amino-6-chloropurine nucleobase was constructed according to method **A** (500 mg, 3.5 mmol of **315**, *n*-BuOH as a solvent, 160°C for 2h in MW reactor). Mobile phase 1-2% methanol in ethyl acetate. Crystallization from ethyl acetate - acetone mixture. Yield 846 mg, 81% as pink ctystals (m.p. = 150-151°C).

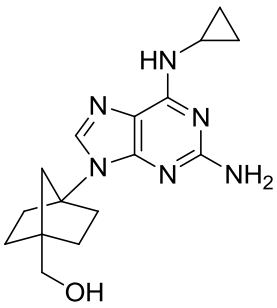
^{1}H NMR (500 MHz, DMSO): δ1.41 (m, 2H, H-2, H-6endo), 1.76 (m, 2H, H-2, H-6exo), 2.02 (m, 2H, H-3exo, H-5exo), 2.04 (bs, 2H, H-7), 2.18 (m, 2H, H-3endo, H-5endo), 3.49 (m, 2H, CH_2O), 4.66 (m, 1H, OH), 6.82 (bs, 2H, NH_2), 8.08 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 31.30 (C-2, C-6), 34.28 (C-3, C-5), 43.34 (C-7), 48.44 (C-1), 64.31 (CH_2O), 65.45 (C-4), 124.27 (C-5'), 142.15 (C-8'), 149.64 (C-6'), 154.55 (C-4'), 159.49 (C-2'). ESI MS *m/z* (%): 294.2 (37) [M+H], 316.2 (19) [M+Na], 608.8 (100) [2M+Na]; HRMS ESI ($C_{13}H_{17}ON_5Cl$) calculated: 294.11161; found: 294.11167. For $C_{13}H_{16}ClN_5O$ (293.75) calculated: 53.15% C, 5.49% H, 23.84% N, 12.07% Cl; found: 53.33% C, 5.56% H, 23.61% N, 12.30% Cl.



[4-(2,6-Diamino-9*H*-purin-9-yl)bicyclo[2.2.1]hept-1-yl]methanol (323)

Ammonolysis was performed according to method **F2** starting from **322** (120 mg, 0.41 mmol). Mobile phase: 15-30% methanol in ethyl acetate. Crystallization from water-methanol mixture. Yield 73 mg, 65%, pale orange crystals (m.p. = 268°C)

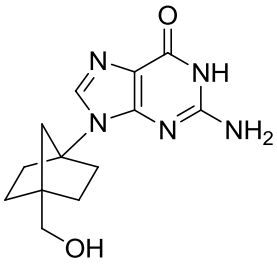
^{1}H NMR (500 MHz, DMSO): δ1.39 (m, 2H, H-2, H-6endo), 1.74 (m, 2H, H-2, H-6exo), 2.00 (bs, 2H, H-7), 2.03 (m, 2H, H-3exo, H-5exo), 2.13 (m, 2H, H-3endo, H-5endo), 3.48 (d, 2H, $J_{CH2,OH}$ = 5.3, CH_2O), 4.61 (t, 1H, $J_{OH,CH2}$ = 5.3, OH), 5.64 (bs, 2H, 2'-NH_2), 6.58 (m, 2H, 6'-NH_2), 7.64 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 31.39 (C-2, C-6), 34.40 (C-3, C-5), 43.44 (C-7), 48.39 (C-1), 64.47 (CH_2O), 64.83 (C-4), 114.32 (C-5'), 136.17 (C-8'), 152.41 (C-4'), 156.32 (C-6'), 159.90 (C-2').ESI MS *m/z* (%): 275.3 (100) [M+H]; HRMS ESI ($C_{13}H_{19}ON_6$) calculated: 275.16149; found: 275.16145 For $C_{13}H_{18}N_6O$ (274.32) calculated: 56.92% C, 6.61% H, 30.64% N; found: 57.00% C, 6.49% H, 30.64% N.



{4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]bicyclo [2.2.1]hept-1-yl}methanol (324)

Nucleophilic displacement performed according to method **G2** starting from **322** (588 mg, 2 mmol). Mobile phase: 5-10% methanol in ethyl acetate. Crystallization from acetone. Yield 502 mg, 80 %, off-white crystals (m.p. = 247°C).

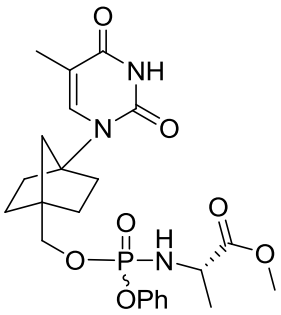
^{1}H NMR (500 MHz, DMSO): δ 0.57 and 0.64 (m, 4H, CH_2-cyclop), 1.39 (m, 2H, H-2, H-6endo), 1.74 (m, 2H, H-2, H-6exo), 2.00 (bs, 2H, H-7), 2.02 (m, 2H, H-3exo, H-5exo), 2.14 (m, 2H, H-3endo, H-5endo), 3.01 (bs, 1H, CH-cyclop), 3.48 (d, 2H, $J_{CH2,OH}$ = 5.0, CH_2O), 4.61 (t, 1H, $J_{OH,CH2}$ = 5.2, OH), 5.70 (bs, 2H, NH_2), 7.18 (m, 1H, NH), 7.63 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.61 (CH_2-cyclop), 31.40 (C-2, C-6), 34.41 (C-3, C-5), 43.46 (C-7), 48.39 (C-1), 64.48 (CH_2O), 64.84 (C-4), 114.58 (C-5'), 135.91 (C-8'), 151.9 (C-4'), 156.10 (C-6'), 159.82 (C-2').ESI MS *m/z* (%): 315.3 (100) [M+H]; HRMS ESI ($C_{16}H_{23}ON_6$) calculated: 315.19279; found: 315.19268. For $C_{16}H_{22}N_6O$ (314.39) calculated: 61.13% C, 7.05% H, 26.73% N; found: 60.95% C, 7.02% H, 26.81% N.



2-Amino-9-[4-(hydroxymethyl)bicyclo[2.2.1]hept-1-yl]-1,9-dihydro-6*H*-purin-6-one (325)

Hydrolysis to guanine derivative was performed according to method **J** starting from **322** (120 mg, 0.41 mmol). Mobile phase: 15-30% methanol in ethyl acetate. Crystallization from water-methanol mixture. Yield 78 mg, 69%, pale brown powder (m.p. > 360°C (decomp)).

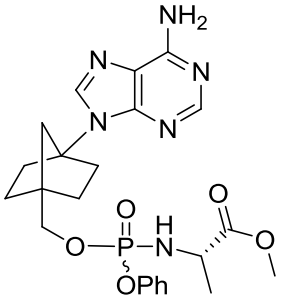
^{1}H NMR (500 MHz, DMSO): δ 1.38 (m, 2H, H-2, H-6endo), 1.73 (m, 2H, H-2, H-6exo), 1.98 (bs, 2H, H-7), 1.98 (m, 2H, H-3exo, H-5exo), 2.15 (m, 2H, H-3endo, H-5endo), 3.47 (d, 2H, $J_{CH2,OH}$ = 5.3, CH_2O), 4.62 (t, 1H, $J_{OH,CH2}$ = 5.3, OH), 6.36 (bs, 2H, NH_2), 7.62 (s, 1H, H-8'), 10.57 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 31.38 (C-2, C-6), 34.53 (C-3, C-5), 43.50 (C-7), 48.37 (C-4), 64.40 (CH_2O), 65.13 (C-1), 117.86 (C-5'), 136.17 (C-8'), 151.75 (C-4'), 152.89 (C-2'), 157.04 (C-6'). ESI MS *m/z* (%): 276.2 (14) [M+H], 298.2 (100) [M+Na]; HRMS ESI ($C_{13}H_{18}O_2N_5$) calculated: 276.14550; found: 276.14549. For $C_{13}H_{17}N_5O_2$ (275.31) calculated: 56.31% C, 6.22% H, 25.44% N; found: 56.24% C, 6.30% H, 25.31% N.



Methyl (2S)-2-[({[4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)bicyclo[2.2.1]heptan-1-yl]methoxy} (phenoxy)phosphoryl)amino]propanoate (326)

Phosphoramidate was prepared according to method **L** starting from **316** (233 mg, 0.93 mmol). Mobile phase: 1-10% methanol in ethyl acetate. Yield 177 mg, 39%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, DMSO): δ 1.23 (m, 3H, NH-CH-*CH$_3$*), 1.41 (m, 2H, H-2b), 1.66 - 1.71 (m, 4H, H-3b, H-2a), 1.76 (t, 3H, $J_{CH3,6}$ = 1.0, 5'-*CH$_3$*), 1.80 - 1.90 (m, 2H, H-7a, H-7b), 2.30 (m, 1H, H-2a), 3.59 and 3.61 (s, 3H, O-CH$_3$), 3.85 (m, 1H, NH-*CH*), 3.98 - 4.06 (m, 2H, 1-CH$_2$-O), 5.97 (m, 1H, NH), 7.15 - 7.22 (m, 3H, H-2'', H-4''), 7.35 - 7.42 (m, 3H, H-6', H-3''), 11.10 (bs, 1H, H-3'). ^{13}C NMR (125.8 MHz, DMSO): δ 12.20 (5'-CH$_3$), 19.81 - 19.89 (m, NH-CH-*CH$_3$*), 30.96 and 31.04 (C-2), 33.19 (C-3), 43.82 and 43.88 (C-7), 45.23 and 45.24 (d, $J_{1\text{-}P}$ = 8.3, C-1), 49.87 and 50.03 (NH-*CH*), 52.02 and 52.05 (O-*CH$_3$*), 69.09 and 69.23 (d, $J_{CH2,P}$ = 5.6, 1-CH$_2$-O), 69.70 and 69.74 (C-4), 107.84 and 107.86 (C-5'), 120.49 and 120.52 (C-2''), 124.67 (C-4''), 129.73 and 129.76 (C-3''), 139.75 and 139.81 (C-6'), 150.94 and 150.96 (C-2'), 150.99 and 151.02 (C-1''), 164.25 and 164.26 (C-4'), 173.90 and 173.93 (COO). ESI MS *m/z* (%): 492.3 (5) [M+H], 514.3 (100) [M+Na]; HRMS ESI ($C_{23}H_{30}O_7N_3NaP$) calculated: 514.17136; found: 514.17143. For $C_{23}H_{30}N_3O_7P$ (491.47) calculated: 56.21% C, 6.15% H, 8.55% N; 6.30% P; found: 56.01% C, 6.18% H, 8.14% N, 6.21% P.

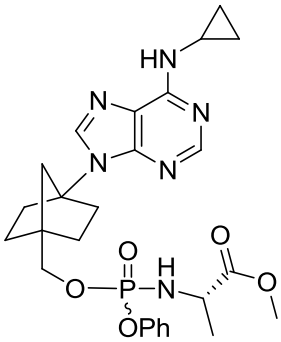


Methyl (2S)-2-[({[4-(6-amino-9H-purin-9-yl)bicyclo[2.2.1] heptan-1-yl]methoxy}(phenoxy)phosphoryl)amino] propanoate (327)

Phosphoramidate was prepared according to method **L** starting from **318** (222 mg, 0.86 mmol). Mobile phase: 5-20% methanol in ethyl acetate. Yield 243 mg, 57%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, DMSO): δ 1.24 (dd, 3H, $J_{CH3,CH}$ = 7.1, $J_{CH3,NH}$ = 0.8, CH-*CH$_3$*), 1.51 (m, 2H, H-2b, H-6b), 1.79 (m, 2H, H-2a, H-6a), 2.06 - 2.23 (m, 6H, H-7, H-3, H-5), 3.60 and 3.62 (s, 3H, O-CH$_3$), 3.86 (m, 1H, NH-*CH*), 4.09 - 4.14 (m, 2H,

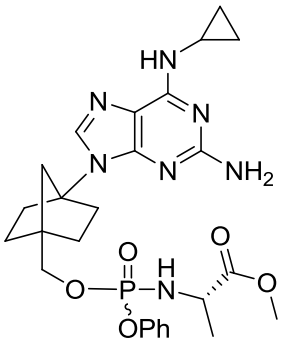
1-CH_2-O), 5.99 (m, 1H, NH), 7.15 - 7.23 (m, 5H, NH_2, H-2'', H-4''), 7.37 (m, 2H, H-3''), 8.07 and 8.08 (s, 1H, H-8'), 8.12 and 8.12 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): δ 19.83 and 19.88 (d, $J_{CH3,P}$ = 5.9, CH-*CH_3*), 31.07 and 31.16 (d, $J_{2,P}$ and $J_{6,P}$ = 1.8 and 4.4, C-2, C-6), 34.28 (C-3, C-5), 43.34 and 43.39 (C-7), 46.54 and 46.60 (d, J_{1-P} = 8.4, C-1), 49.89 and 50.05 (NH-*CH*), 52.04 and 52.07 (O-*CH_3*), 65.21 and 65.23 (C-4), 69.00 and 69.15 (d, $J_{CH2,P}$ = 5.4, 1-CH_2-O), 119.78 (C-5'), 120.49 and 120.53 (C-2''), 124.68 (C-4''), 129.74 and 129.77 (C-3''), 139.53 and 139.54 (C-8'), 150.08 (C-4'), 150.97 and 151.00 (d, $J_{1'',P}$ = 6.5, C-1''), 152.23 (C-2'), 156.30 (C-6'), 173.93 and 173.96 (COO). ESI MS *m/z* (%): 501.2 (100) [M+H], 523.2 (63) [M+Na]; HRMS ESI ($C_{23}H_{30}O_5N_6P$) calculated: 501.20098; found: 501.20091.



Methyl (2S)-2-[({[4-(6-(cyclopropylamino)-9H-purin-9-yl) bicyclo[2.2.1]heptan-1-yl]methoxy}(phenoxy)phosphoryl) amino]propanoate (328)

Phosphoramidate was prepared according to method **L** starting from **319** (160 mg, 0.53 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Yield 80 mg, 28%, white foam.

^{1}H NMR (500 MHz, DMSO): 0.60 and 0.71 (m, 4H, CH_2-cyclop), 1.22 – 1.25 (m, 3H, CH-**CH_3**), 1.51 and 1.80 (m, 4H, H-2, H-6), 2.07 – 2.25 (m, 6H, H-3, H-5, H-7), 3.01 (bs, 1H, CH-cyclop), 3.60 and 3.62 (s, 3H, OCH_3), 3.82 – 3.89 (m, 1H, CH-COO), 4.05 – 4.14 (m, 2H, CH_2-O), 5.97 (dd, 0,5H, J_{H-N-P} = 12.7, J_{NH-CH} = 10.0, P-NH), and 6.03 (dd, 0,5H, J_{H-N-P} = 13.5, J_{NH-CH} = 10.1, P-NH), 7.13-7.26 (m, 3H, H-2'', H-4''), 7.35 – 7.39 (m, 2H, H-3''), 7.82 and 7.84 (bs, 1H, 6'-NH), 8.08 and 8.09 (s, 1H, H-8'), 8.22 and 8.23 (bs, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 6.60 (CH_2-cyclop), 19.86 (CH-CH_3), 31.16 and 31.39 (C-2), 34.29 and 34.61 (C-3, C-5), 43.35 and 43.41 (C-7), 46.57 and 46.59 (d, J_{1-P} = 8.3, C-1), 49.89 and 50.05 (CH-COO), 52.05 and 52.08 (OCH_3), 65.26 and 65.40 (C-4), 68.97 and 69.13 (CH_2O), 120.16 (C-5'), 120.50 and 120.53 (C-2''), 124.69 (C-4''), 129.76 and 129.78 (C-3''), 139.40 and 139.44 (C-8'), 149.50 (C-4'), 151.00 (C-1''), 152.14 (C-2'), 155.84 (C-6'), 173.94 and 173.97 (COO). HRMS ESI ($C_{26}H_{34}N_6O_5P$) calculated: 541.2323, found: 541.2322.

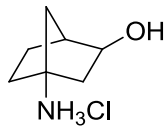


Methyl (2S)-2-{[({4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]heptan-1-yl}methoxy)(phenoxy) phosphoryl]amino}propanoate (329)

Phosphoramidate was prepared according to method **L** starting from **324** (350 mg, 1.11 mmol). Mobile phase: 5-20% methanol in ethyl acetate. Yield 395 mg, 64%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, DMSO): δ 0.61 (m, 4H, CH_2-cyclop), 1.24 (dd, 3H, $J_{CH3,CH}$ = 7.1, $J_{CH3,NH}$ = 1.0, CH-*CH_3*), 1.48 (m, 2H, H-2b, H-6b), 1.75 (m, 2H, H-2a, H-6a), 2.00 - 2.09 (m, 4H, H-7, H-3b, H-5b), 2.16 (bs, 2H, H-3a, H-5a), 3.01 (bs, 1H, CH-cyclop), 3.60 and 3.62 (s, 3H, O-CH_3), 3.86 (m, 1H, NH-*CH*), 4.06 - 4.12 (m, 2H, 1-CH_2-O), 5.71 (bs, 2H, NH_2), 5.99 (m, 1H, NH), 7.15 - 7.24 (m, 3H, H-2'', H-4''), 7.35 - 7.40 (m, 2H, H-3''), 7.62 and 7.64 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.59 (CH_2-cyclop), 19.82 and 19.88 (d, $J_{CH3,P}$ = 6.8, CH-*CH_3*), 24.5 (CH-cyclop), 31.13 and 31.21 (C-2, C-6), 33.12 (C-3, C-5), 43.21 and 43.28 (C-7), 46.48 and 46.50 (d, $J_{1\text{-}P}$ = 8.3, C-1), 49.89 and 50.04 (NH-*CH*), 52.04 and 52.07 (O-*CH_3*), 64.69 and 64.72 (C-4), 69.13 and 69.29 (d, $J_{CH2,P}$ = 5.4, 1-CH_2-O), 114.55 (C-5'), 120.50 and 120.53 (C-2''), 124.68 (C-4''), 129.74 and 129.77 (C-3''), 135.82 (C-8'), 150.96 and 150.99 (d, $J_{1'',P}$ = 6.5, C-1''), 151.9 (C-4'), 156.12 (C-6'), 159.87 (C-2'), 173.94 and 173.97 (COO). ESI MS *m/z* (%): 556.4 (100) [M+H], 578.4 (37) [M+Na]; HRMS ESI ($C_{26}H_{35}O_5N_7P$) calculated: 556.24318; found: 556.24281.

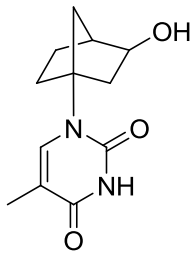
5.7. Carbocyclic nucleoside analogues locked in South conformation



(1*S,2*S**,4*S**)-4-Aminobicyclo[2.2.1]heptan-2-ol hydrochloride (330)**

Curtius rearrangement was performed according to **Method D** starting from **278** (3 g, 19.2 mmol). Yield 2.35 g, 74%, white solid, used for subsequent reactions without further purification. Analytical sample was crystallized from ethanol/diethylether mixture.

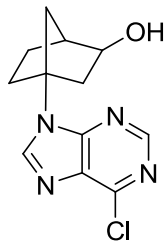
^{1}H NMR (500 MHz, DMSO): 1.01 (ddt, 1H, J_{gem} = 8.9, $J_{7a\text{-}3en}$ = 2.5, $J_{7a\text{-}1}$ = $J_{7a\text{-}2}$ = 1.5, H-7a), 1.05 - 1.12 (m, 2H, H-5endo, H-6endo), 1.16 (ddd, 1H, J_{gem} = 12.4, $J_{3ex\text{-}5ex}$ = 3.6, $J_{3ex\text{-}2}$ = 2.6, H-3exo), 1.27 (m, 1H, H-5exo), 1.43 - 1.55 (m, 2H, H-6exo, H-7b), 1.62 (ddd, 1H, J_{gem} = 12.4, $J_{3en\text{-}2}$ = 7.0, $J_{3en\text{-}7a}$ = 2.4, H-3endo), 1.84 (dm, 1H, $J_{1\text{-}6ex}$ = 5.1, H-1), 3.62 (dm, 1H, $J_{2\text{-}3en}$ = 7.0, H-2). ^{13}C NMR (125.8 MHz, DMSO): 25.22 (C-6), 35.37 (C-5), 41.75 (C-7), 43.63 (C-1), 48.87 (C-3), 61.41 (C-4), 73.80 (C-2). HRMS ($C_7H_{14}NO$) calculated: 128.1075, found: 128.1070 (M+H).



1-[(1*R,3*R**,4*R**)-3-Hydroxybicyclo[2.2.1]hept-1-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (331)**

Thymine nucleobase construction was performed according to method **E** starting from **315** (225 mg, 1.38 mmol). Mobile phase: 1-5% methanol in ethyl acetate. Crystallization from toluene. Yield 200 mg, 61%, colorless needles (m.p. = 256°C).

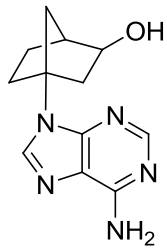
^{1}H NMR (500 MHz, DMSO): δ 1.22 (m, 1H, H-6endo), 1.29 (dm, 1H, J_{gem} = 12.8, H-3exo), 1.44 (m, 1H, H-5exo), 1.66 (tdd, 1H, J_{gem} = $J_{6ex,5ex}$= 12.5, $J_{6ex,1}$ = 5.3, $J_{6ex,5en}$ = 4.2, H-6exo), 1.74 (dm, 1H, J_{gem} = 9.1, H-7a), 1.77 (d, 3H, $J_{CH3,6'}$ = 1.2, CH_3), 2.01 - 2.07 (m, 2H, H-1, H-5endo), 2.15 (dm, 1H, J_{gem} = 9.1, H-7b), 2.58 (ddd, 1H, J_{gem} = 12.8, $J_{3en,2}$ = 7.0, $J_{3en,7a}$ = 2.4, H-3endo), 3.73 (m, 1H, H-2), 4.76 (d, 1H, $J_{OH,2}$ = 3.6, OH), 7.51 (q, 1H, $J_{6',CH3}$ = 1.2, H-6'), 11.08 (bs, 1H, H-3'). ^{13}C NMR (125.8 MHz, DMSO): δ 12.18 (CH_3), 24.20 (C-6), 31.41 (C-5), 38.00 (C-7), 41.53 (C-1), 44.97 (C-3), 68.97 (C-4), 72.71 (C-2), 107.82 (C-5'), 139.99 (C-6'), 151.06 (C-2'), 164.30 (C-4'). ESI MS *m/z* (%): 259.1 (100) [M+H], 281.1 (55) [M+Na]; HRMS ESI ($C_{12}H_{17}N_2O_3$) calculated: 237.12337, found: 237.12339. For $C_{12}H_{16}N_2O_3$ (236.27) calculated: 61.00% C, 6.83% H, 11.86 % N; found: 61.27% C, 6.98% H, 11.72 % N.



(1*S,2*S**,4*S**)-4-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (332)**

6-Chloropurine nucleobase was constructed according to method **C2** (2.3 g, 14 mmol of **330**, EtOH as a solvent, 105°C for 7d in sealed vessel). Mobile phase toluene - ethyl acetate = 1:4 and then ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 2.1 g, 55% as white ctystals (m.p. = 155-157°C).

^{1}H NMR (500 MHz, DMSO): 1.35 (dddd, 1H, J_{gem} = 12.4, $J_{6en-5en}$ = 9.2, $J_{6en-5ex}$ = 4.8, J_{6en-7b} = 2.1, H-6endo), 1.75 (dm, 1H, J_{gem} = 12.4, H-3exo), 1.79 (tdd, 1H, J_{gem} = $J_{6ex-5ex}$ = 12.3, J_{6ex-1} = 5.1, $J_{6ex-5en}$ = 4.2, H-6exo), 1.90 (m, 1H, H-5exo), 2.01 (dddd, 1H, J_{gem} = 11.3, $J_{5en-6en}$ = 9.1, $J_{5en-6ex}$ = 4.1, J_{5en-7b} = 2.3, H-5endo), 2.05 (dm, 1H, J_{gem} = 9.1, H-7a), 2.19 (dm, 1H, J_{1-6ex} = 5.0, H-1), 2.49 (m, 1H, H-7b), 2.54 (ddd, 1H, J_{gem} = 12.5, J_{3en-2} = 6.9, J_{3en-7a} = 2.4, H-3endo), 3.87 (m, 1H, H-2), 4.93 (d, 1H, J_{OH-2} = 3.5, OH), 8.71 (s, 1H, H-8'), 8.77 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 24.04 (C-6), 32.65 (C-5), 37.57 (C-7), 42.69 (C-1), 45.85 (C-3), 65.17 (C-4), 72.67 (C-2), 131.72 (C-5'), 146.59 (C-8'), 149.37 (C-6'), 151.28 (C-2'), 152.43 (C-4'). ESI MS *m/z* (%): 265.2 (100) [M+H]. For $C_{12}H_{13}N_4OCl$ (262.69) calculated: 54.45% C, 4.95% H, 21.17% N, 13.39% Cl; found: 54.49% C, 5.08% H, 21.26% N, 12.99% Cl.

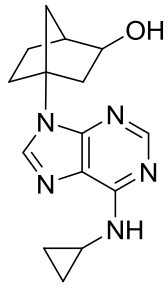


(1*S,2*S**,4*S**)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (333)**

Ammonolysis was performed according to method **F1** starting from **332** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water. Yield 100 mg, 83%, colorless needles (m.p. = 253°C).

^{1}H NMR (500 MHz, DMSO): 1.31 (dddd, 1H, J_{gem} = 12.4, $J_{6en-5en}$ = 9.1, $J_{6en-5ex}$ = 4.7, J_{6en-7b} = 2.1, H-6endo), 1.69 (dm, 1H, J_{gem} = 12.4, H-3exo), 1.75 (tdd, 1H, J_{gem} = $J_{6ex-5ex}$ = 12.3, J_{6ex-1} = 5.0, $J_{6ex-5en}$ = 4.2, H-6exo), 1.85 (m, 1H, H-5exo), 1.94 (dddd, 1H, J_{gem} = 11.3, $J_{5en-6en}$ = 9.1, $J_{5en-6ex}$ = 4.1, J_{5en-7b} = 2.2, H-5endo), 2.00 (dm, 1H, J_{gem} = 9.1, H-7a), 2.15 (dm, 1H, J_{1-6ex} = 5.0, H-1), 2.39 (dq, 1H, J_{gem} = 9.1, J_{7b-1} = J_{7b-5en} = J_{7b-6en} = 2.0, H-7b), 2.49 (ddd, 1H, J_{gem} = 12.6, J_{3en-2} = 6.8, J_{3en-7a} = 2.4, H-3endo), 3.84 (m, 1H, H-2), 4.88 (d, 1H, J_{OH-2} = 3.5, OH), 7.19 (bs, 2H, NH_2), 8.116 and 8.120 (s, 2H, H-2', H-8'). ^{13}C NMR (125.8 MHz, DMSO): 24.22 (C-6), 32.73 (C-5), 37.61 (C-7), 42.75 (C-1), 46.02 (C-3), 64.38 (C-4), 72.81 (C-2), 119.82 (C-5'),

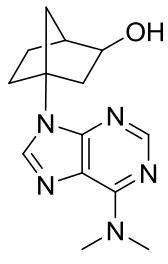
139.74 (C-8'), 150.24 (C-4'), 152.27 (C-2'), 156.31 (C-6'). ESI MS *m/z* (%): 246.2 (100) [M+H], 268.1 (21) [M+Na]. For $C_{12}H_{15}N_5O$ (245.28) calculated: 58.76% C, 6.16% H, 28.55% N; found: 58.48% C, 6.17% H, 28.28% N.



(1*S,2*S**,4*S**)-4-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo [2.2.1]heptan-2-ol (334)**

Nucleophilic displacement performed according to method **G1** starting from **332** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene-cyclohexane mixture. Yield 123 mg, 88 %, white crystals (m.p. = 155-156°C).

^{1}H NMR (500 MHz, DMSO): 0.60 and 0.71 (m, 4H, CH_2-cyklop), 1.31 (dddd, 1H, J_{gem} = 12.3, $J_{6en-5en}$ = 9.0, $J_{6en-5ex}$ = 4.8, J_{6en-7b} = 2.0, H-6endo), 1.69 (dm, 1H, J_{gem} = 12.5, H-3exo), 1.75 (tdd, 1H, J_{gem} = $J_{6ex-5ex}$ = 12.3, J_{6ex-1} = 5.0, $J_{6ex-5en}$ = 4.2, H-6exo), 1.85 (m, 1H, H-5exo), 1.94 (dddd, 1H, J_{gem} = 11.3, $J_{5en-6en}$ = 9.2, $J_{5en-6ex}$ = 4.1, J_{5en-7b} = 2.2, H-5endo), 2.00 (dm, 1H, J_{gem} = 9.1, H-7a), 2.15 (dm, 1H, J_{1-6ex} = 4.9, H-1), 2.39 (dm, 1H, J_{gem} = 9.1, H-7b), 2.50 (ddd, 1H, J_{gem} = 12.5, J_{3en-2} = 6.9, J_{3en-7a} = 2.4, H-3endo), 2.99 (bs, 1H, CH-cyklop), 3.84 (m, 1H, H-2), 4.88 (d, 1H, J_{OH-2} = 3.5, OH), 7.86 (bs, 1H, NH), 8.12 (s, 1H, H-8'), 8.22 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 6.61 (CH_2-cyklop), 24.23 (C-6), 32.75 (C-5), 37.63 (C-7), 42.75 (C-1), 46.03 (C-3), 64.40 (C-4), 72.81 (C-2), 120.20 (C-5'), 139.59 (C-8'), 149.69 (C-4'), 152.18 (C-2'), 155.88 (C-6'). ESI MS *m/z* (%): 286.2 (100) [M+H], 308.2 (12) [M+Na]. For $C_{15}H_{19}N_5O$ (285.16) calculated: 63.14% C, 6.71% H, 24.54% N; found: 62.86% C, 6.83% H, 24.24% N.

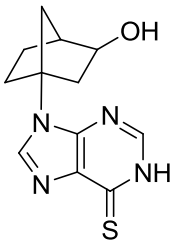


(1*S,2*S**,4*S**)-4-[6-(Dimethylamino)-9H-purin-9-yl]bicyclo[2.2.1] heptan-2-ol (335)**

Nucleophilic displacement performed according to method **H2** starting from **332** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 116 mg, 86 %, white crystals (m.p. = 143°C).

^{1}H NMR (500 MHz, DMSO): 1.31 (dddd, 1H, J_{gem} = 12.3, $J_{6en-5en}$ = 9.2, $J_{6en-5ex}$ = 4.7, J_{6en-7b} = 2.1, H-6endo), 1.68 (dm, 1H, J_{gem} = 12.4, H-3exo), 1.75 (tdd, 1H, J_{gem} = $J_{6ex-5ex}$ = 12.3, J_{6ex-1} = 5.1, $J_{6ex-5en}$ = 4.0, H-6exo), 1.84 (m, 1H, H-5exo), 1.95 (dddd,

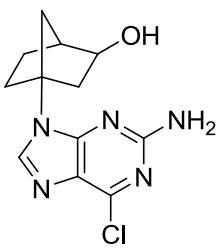
1H, J_{gem} = 11.3, $J_{5en-6en}$ = 9.4, $J_{5en-6ex}$ = 4.1, J_{5en-7b} = 2.2, H-5endo), 2.01 (dm, 1H, J_{gem} = 9.0, H-7a), 2.15 (dm, 1H, J_{1-6ex} = 5.0, H-1), 2.39 (dq, 1H, J_{gem} = 9.1, J_{7b-1} = J_{7b-5en} = J_{7b-6en} = 2.0, H-7b), 2.51 (ddd, 1H, J_{gem} = 12.4, J_{3en-2} = 6.9, J_{3en-7a} = 2.4, H-3endo), 3.44 (bs, 6H, CH_3), 3.84 (m, 1H, H-2), 4.88 (d, 1H, J_{OH-2} = 3.6, OH), 8.12 (s, 1H, H-8'), 8.19 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 24.21 (C-6), 32.59 (C-5), 37.54 (C-7), 42.69 (C-1), 45.91 (C-3), 64.42 (C-4), 72.78 (C-2), 120.36 (C-5'), 138.58 (C-8'), 151.07 (C-4'), 151.55 (C-2'), 154.53 (C-6'). ESI MS *m/z* (%): 274.2 (100) [M+H], 296.1 (43) [M+Na]. For $C_{14}H_{19}N_5O$ (273.33) calculated: 61.52% C, 7.01% H, 25.62% N; found: 61.43% C, 7.04% H, 25.26% N.



(1*S,2*S**,4*S**)-4-(6-Sulfanyl-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (336)**

Nucleophilic displacement performed according to method **I** starting from **332** (130 mg, 0.5 mmol). Yield 98 mg, 76%, white powder (m.p. > 320°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): 1.31 (dddd, 1H, J_{gem} = 12.1, $J_{6en-5en}$ = 8.8, $J_{6en-5ex}$ = 4.6, J_{6en-7b} = 2.1, H-6endo), 1.67 (dm, 1H, J_{gem} = 12.5, H-3exo), 1.75 (tdd, 1H, J_{gem} = $J_{6ex-5ex}$ = 12.1, J_{6ex-1} = 5.1, $J_{6ex-5en}$ = 4.0, H-6exo), 1.83 (m, 1H, H-5exo), 1.95 (m, 1H, H-5endo), 1.98 (dm, 1H, J_{gem} = 9.1, H-7a), 2.16 (dm, 1H, J_{1-6ex} = 5.0, H-1), 2.40 (dq, 1H, J_{gem} = 9.2, J_{7b-1} = J_{7b-5en} = J_{7b-6en} = 2.0, H-7b), 2.49 (ddd, 1H, J_{gem} = 12.4, J_{3en-2} = 6.8, J_{3en-7a} = 2.4, H-3endo), 3.84 (dm, 1H, J_{2-3en} = 6.5, H-2), 4.92 (bs, 1H, OH), 8.18 (d, 1H, $J_{2'-1'}$ = 3.8, H-2'), 8.29 (s, 1H, H-8'), 13.74 (bs, 1H, H-1').^{13}C NMR (125.8 MHz, DMSO): 24.14 (C-6), 32.94 (C-5), 37.70 (C-7), 42.71 (C-1), 46.13 (C-3), 64.87 (C-4), 72.73 (C-2), 136.05 (C-5'), 142.17 (C-8'), 144.47 (C-2'), 144.78 (C-4'), 176.07 (C-6'). ESI MS *m/z* (%): 263.1 (12) [M+H], 285.1 (100) [M+Na]. For $C_{12}H_{14}N_4OS$ (262.33) calculated: 54.94% C, 5.38% H, 21.36% N, 12.22% S; found: 54.64% C, 5.37% H, 21.09% N, 12.12% S.

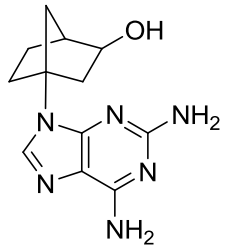


(1*R,2*R**,4*R**)-4-(2-Amino-6-chloro-9*H*-purin-9-yl) bicyclo[2.2.1]heptan-2-ol (337)**

2-Amino-6-chloropurine nucleobase was constructed according to method **A** (2.2 g, 9.6 mmol of **330**, *n*-BuOH as a solvent, 160°C for 3h in MW reactor). Mobile phase 2-10% methanol in ethyl

acetate. Crystallization from toluene. Yield 1.4 g, 63% as off-white ctystals (m.p. = 218°C (decomp.)).

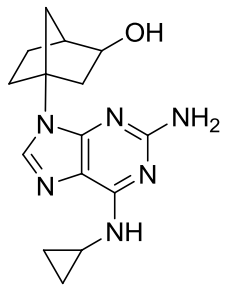
^{1}H NMR (500 MHz, DMSO): δ 1.29 (m, 1H, H-6endo), 1.62 (dm, 1H, J_{gem} = 12.5, H-3exo), 1.70 - 1.83 (m, 2H, H-5exo, H-6exo), 1.93 (m, 1H, H-5endo), 2.01 (dm, 1H, J_{gem} = 9.1, H-7a), 2.15 (m, 1H, H-1); 2.35 (dm, 1H, J_{gem} = 9.2, H-7b), 2.51 (ddd, 1H, J_{gem} = 12.5, $J_{3en,2}$ = 6.9, $J_{3en,7}$ = 2.6, H-3endo), 3.82 (m, 1H, H-2), 4.87 (t, 1H, J_{OH-CH2} = 3.5, OH), 6.79 (bs, 2H, NH_2), 8.11 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.13 (C-6), 32.41 (C-5), 37.38 (C-7), 42.64 (C-1), 45.79 (C-3), 64.41 (C-4), 72.69 (C-2), 124.26 (C-5'), 142.21 (C-8'), 149.66 (C-6'), 154.65 (C-4'), 159.49 (C-2'). ESI MS *m/z* (%): 280.1 (97) [M+H], 302.1 (100) [M+Na]; HRMS ESI ($C_{12}H_{14}N_5OCl$) calculated: 280.09596, found: 280.09595. For $C_{12}H_{14}ClN_5O$ (279.73) calculated: 51.52% C, 5.04% H, 12.67% Cl, 25.04 % N; found: 51.55% C, 5.05% H, 12.59% Cl, 25.10 % N.



(1*S,2*S**,4*S**)-4-(2,6-diamino-9*H*-purin-9-yl)bicyclo[2.2.1] heptan-2-ol (338)**

Ammonolysis was performed according to method **F2** starting from **337** (220 mg, 0.79 mmol). Mobile phase: 10-15% methanol in ethyl acetate. Crystallization from water-methanol mixture. Yield 170 mg, 83%, pale orange crystals (m.p. = 295°C).

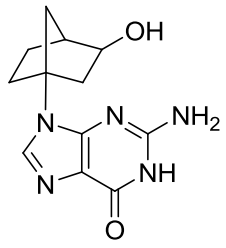
^{1}H NMR (500 MHz, DMSO): δ 1.27 (m, 1H, H-6endo), 1.59 (dm, 1H, J_{gem} = 12.6, H-3exo), 1.68 - 1.81 (m, 2H, H-5exo, H-6exo), 1.89 (m, 1H, H-5endo), 2.00 (dm, 1H, J_{gem} = 9.1, H-7a), 2.12 (m, 1H, H-1); 2.28 (dm, 1H, J_{gem} = 9.1, H-7b), 2.49 (m, 1H, H-3endo), 3.80 (m, 1H, H-2), 4.82 (m, 1H, OH), 5.63 (bs, 2H, 2'-NH_2), 6.60 (bs, 2H, 6'-NH_2), 7.68 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.27 (C-6), 32.51 (C-5), 37.44 (C-7), 42.66 (C-1), 45.98 (C-3), 63.82 (C-4), 72.79 (C-2), 114.28 (C-5'), 136.27 (C-8'), 152.53 (C-4'), 156.33 (C-6'), 159.91 (C-2'). ESI MS *m/z* (%): 261.3 (100) [M+H], 283.3 (14) [M+Na]; HRMS ESI ($C_{12}H_{17}ON_6$) calculated: 261.14584; found: 261.14578. For $C_{12}H_{16}N_6O$ (260.30) calculated: 55.37% C, 6.20% H, 32.29% N; found: 55.21% C, 6.29% H, 32.59% N.



(1*R,2*R**,4*R**)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.1]heptan-2-ol (339)**

Nucleophilic displacement performed according to method **G2** starting from **337** (490 mg, 1.75 mmol). Poorly soluble product was filtered off and thoroughly washed with water and methanol. Yield 400 mg, 76 %, pink crystals (m.p. = 258°C (decomp.)).

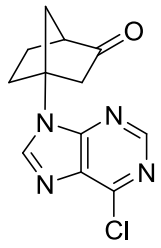
^{1}H NMR (500 MHz, DMSO): δ 0.57 and 0.65 (m, 4H, CH_2-cyclop), 1.27 (m, 1H, H-6endo), 1.58 (dm, 1H, J_{gem} = 12.5, H-3exo), 1.68 - 1.80 (m, 2H, H-5exo, H-6exo), 1.89 (m, 1H, H-5endo), 2.00 (m, 1H, J_{gem} = 9.1, H-7a), 2.12 (m, 1H, H-1), 2.28 (dm, 1H, J_{gem} = 9.2, H-7b), 2.50 (m, 1H, H-3endo), 3.01 (bs, 1H, CH-cyclop), 3.80 (m, 1H, H-2), 4.81 (d, 1H, $J_{OH,2}$ = 3.6, OH), 5.69 (bs, 2H, NH_2), 7.21 (bs, 1H, NH), 7.66 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.58 (CH_2-cyclop), 24.27 (C-6), 32.51 (C-5), 37.44 (C-7), 42.65 (C-1), 45.98 (C-3), 63.80 (C-4), 72.78 (C-2), 114.54 (C-5'), 135.96 (C-8'), 152.1 (C-4'), 156.08 (C-6'), 159.82 (C-2'). ESI MS *m/z* (%): 301.3 (100) [M+H], 323.3 (10) [M+Na]; HRMS ESI ($C_{15}H_{21}ON_6$) calculated: 301.17714; found: 301.17697. For $C_{15}H_{20}N_6O$ (300.36) calculated: 59.98% C, 6.71% H, 27.98% N; found: 60.11% C, 6.80% H, 27.80% N.



2-Amino-9-[(1*R,3*R**,4*R**)-3-hydroxybicyclo[2.2.1]hept-1-yl]-1,9-dihydro-6*H*-purin-6-one (340)**

Hydrolysis to guanine derivative was performed according to method **J** starting from **337** (100 mg, 0.36 mmol). Yield 52 mg, 56%, pale orange powder (m.p. > 360°C).

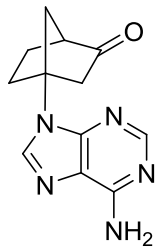
^{1}H NMR (500 MHz, DMSO): δ 1.25 (m, 1H, H-5endo), 1.56 (dm, 1H, J_{gem} = 12.6, H-2exo), 1.67 - 1.77 (m, 2H, H-6exo, H-5exo), 1.89 (m, 1H, H-6endo), 1.97 (dm, 1H, J_{gem} = 9.2, H-7a), 2.11 (m, 1H, H-4); 2.27 (dm, 1H, J_{gem} = 9.2, H-7b), 2.48 (ddd, 1H, J_{gem} = 12.5, $J_{2en,3}$ = 6.9, $J_{2en,7a}$ = 2.3, H-2endo), 3.79 (m, 1H, H-3), 4.82 (m, 1H, OH), 6.36 (bs, 2H, NH_2), 7.66 (s, 1H, H-8'), 10.10 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.24 (C-5), 32.64 (C-6), 37.50 (C-7), 42.62 (C-4), 46.04 (C-2), 64.08 (C-1), 72.76 (C-3), 117.83 (C-5'), 136.25 (C-8'), 151.88 (C-4'), 152.94 (C-2'), 157.08 (C-6'). ESI MS *m/z* (%): 262.2 (52) [M+H], 284.2 (100) [M+Na]; HRMS ESI ($C_{12}H_{16}O_2N_5$) calculated: 262.12985, found: 262.12983. For $C_{12}H_{15}N_5O_2$ (261.28) calculated: 55.16% C, 5.79% H, 26.80% N; found: 55.09% C, 5.77% H, 26.71% N.



(1*S,4*S**)-4-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-one (341)**

A solution of **332** (1 g, 3.8 mmol) in dichlormethane (50 mL) was added dropwise to a suspension of PDC (2.84 g, 7.6 mmol) and crushed molecular sieves (3 g) in dichlormethane (50 mL). Reaction mixture was stirred 7 days at RT, solid parts were filtered off and thoroughly washed with chloroform. Resulting brown oil was adsorbed on silica gel and chromatographed on a short column (ethyl acetate - toluene - acetone - ethanol 17:4:3:1). Crystallization from water - methanol mixture afforded **341** (830 mg, 82%) as white crystals (m.p. = 167°C).

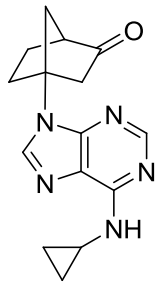
^{1}H NMR (500 MHz, DMSO): 1.58 (m, 1H, H-6endo), 2.12 (tt, 1H, $J_{gem} = J_{6ex-5ex}$ = 12.6, $J_{6ex-1} = J_{6ex-5en}$ = 4.9, H-6exo), 2.27 (m, 1H, H-5exo), 2.34 (dddd, 1H, J_{gem} = 11.7, $J_{5en-6en}$ = 9.0, $J_{5en-6ex}$ = 4.8, J_{5en-7} = 2.0, H-5endo), 2.52 - 2.60 (m, 2H, H-7), 2.79 (dm, 1H, J_{1-6ex} = 5.0, H-1), 2.85 – 2.86 (m, 2H, H-3), 8.77 (s, 1H, H-8'), 8.80 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 23.31 (C-6), 31.68 (C-5), 39.95 (C-7), 48.60 (C-3), 49.00 (C-1), 63.47 (C-4), 131.74 (C-5'), 146.37 (C-8'), 149.49 (C-6'), 151.48 (C-2'), 152.35 (C-4') 211.07 (C-2). ESI MS *m/z* (%): 263.1 (100) [M+H], 285.1 (4) [M+Na]. For $C_{12}H_{11}N_4OCl$ (262.69) calculated: 54.87% C, 4.22% H, 21.33% N, 13.50% Cl; found: 54.70% C, 4.21% H, 20.99% N, 13.39% Cl.



(1*S,4*S**)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-one (342)**

Ammonolysis was performed according to method **F1** starting from **341** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water - methanol mixture. Yield 93 mg, 77%, colorless crystals (m.p. = 239°C)

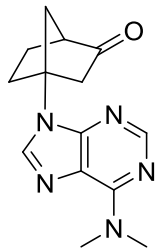
^{1}H NMR (500 MHz, DMSO): 1.54 (m, 1H, H-6endo), 2.09 (m, 1H, H-6exo), 2.21 – 2.30 (m, 2H, H-5), 2.46 – 2.52 (m, 2H, H-7), 2.71 (m, 1H, H-1), 2.75 – 2.85 (m, 2H, H-3), 7.25 (bs, 2H, NH_2), 8.14 (s, 1H, H-2'), 8.19 (s, 1H, H-8').^{13}C NMR (125.8 MHz, DMSO): 23.40 (C-6), 31.64 (C-5), 39.99 (C-7), 48.64 (C-3), 49.08 (C-1), 62.79 (C-4) 119.73 (C-5'), 139.44 (C-8'), 150.08 (C-4'), 152.44 (C-2'), 156.35 (C-6'), 211.68 (C-2),. ESI MS *m/z* (%): 244.1 (100) [M+H]. For $C_{12}H_{13}N_5O$ (243.26) calculated: 59.25% C, 5.39% H, 28.79% N, found: 58.96% C, 5.35% H, 28.45% N.



(1*S,4*S**)-4-[6-(Cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.1] heptan-2-one (343)**

Nucleophilic displacement performed according to method **G1** starting from **341** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene-cyclohexane mixture. Yield 104 mg, 77 %, white crystals (m.p. = 173-174°C).

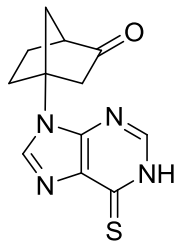
^{1}H NMR (500 MHz, DMSO): 0.61 and 0.72 (m, 4H, CH_2-cyklop), 1.55 (m, 1H, H-6endo), 2.10 (m, 1H, H-6exo), 2.20 – 2.30 (m, 2H, H-5), 2.47 – 2.52 (m, 2H, H-7), 2.72 (dm, 1H, $J_{1\text{-}6ex}$ = 5.2, H-1), 2.75 – 2.85 (m, 2H, H-3), 3.02 (bs, 1H, CH-cyklop), 7.91 (bs, 1H, NH), 8.19 (s, 1H, H-8'), 8.24 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 6.58 (CH_2-cyklop), 23.41 (C-6), 31.65 (C-5), 39.99 (C-7), 48.66 (C-3), 49.07 (C-1), 62.80 (C-4), 120.12 (C-5'), 139.29 (C-8'), 149.63 (C-4'), 152.34 (C-2'), 155.85 (C-6'), 211.67 (C-2). ESI MS *m/z* (%): 284.2 (100) [M+H]. For $C_{15}H_{17}N_5O$ (283.32) calculated: 63.59% C, 6.05% H, 24.72% N, found: 63.33% C, 6.04% H, 24.36% N.



(1*S,4*S**)-4-[6-(Dimethylamino)-9*H*-purin-9-yl]bicyclo[2.2.1] heptan-2-one (344)**

Nucleophilic displacement performed according to method **H2** starting from **341** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 116 mg, 86 %, white crystals (m.p. = 160-161°C).

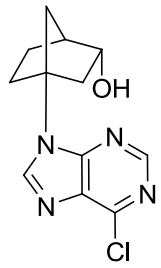
^{1}H NMR (500 MHz, DMSO): 1.55 (m, 1H, H-6endo), 2.10 (m, 1H, H-6exo), 2.19 – 2.31 (m, 2H, H-5), 2.28 (m, 2H, H-3), 2.49 (m, 2H, H-7), 2.71 (dm, 1H, $J_{1\text{-}6ex}$ = 5.1, H-1), 3.46 (bs, 6H, CH_3), 8.19 (s, 1H, H-8'), 8.22 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 23.40 (C-6), 31.53 (C-5), 38.16 (CH_3), 39.91 (C-7), 48.55 (C-3), 49.03 (C-1), 62.82 (C-4), 120.28 (C-5'), 138.29 (C-8'), 150.91 (C-4'), 151.73 (C-2'), 154.55 (C-6'), 211.65 (C-2). ESI MS *m/z* (%): 272.2 (100) [M+H]. For $C_{14}H_{17}N_5O$ (271.31) calculated: 61.98% C, 6.32% H, 25.81% N, found: 61.55% C, 6.33% H, 25.52% N.



(1*S,4*S**)-4-(6-Sulfanyl-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-one (345)**

Nucleophilic displacement performed according to method **I** starting from **341** (130 mg, 0.5 mmol). Yield 115 mg, 89%, white powder (m.p. > 320°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): 1.55 (m, 1H, H-6endo), 2.09 (tt, 1H, $J_{gem} = J_{6ex-5ex}$ = 12.5, $J_{6ex-1} = J_{6ex-5en}$ = 4.9, H-6exo), 2.20 (m, 1H, H-5exo), 2.27 (m, 1H, J_{gem} = 11.7, $J_{5en-6en}$ = 9.0, $J_{5en-6ex}$ = 4.8, J_{5en-7} = 1.9, H-5endo), 2.46 – 2.50 (m, 2H, H-7), 2.73 (dm, 1H, J_{1-6ex} = 4.9, H-1), 2.78 – 2.79 (m, 2H, H-3), 8.19 (bd, 1H, $J_{2'-1'}$ = 1.8, H-2'), 8.34 (s, 1H, H-8'), 13.77 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): 23.37 (C-6), 31.92 (C-5), 40.05 (C-7), 48.78 (C-3), 49.00 (C-1), 63.18 (C-4), 136.04 (C-5'), 141.82 (C-8'), 144.64 (C-4'), 144.72 (C-2'), 176.20 (C-6'), 211.22 (C-2). ESI MS *m/z* (%): 261.1 (18) [M+H], 283.1 (100) [M+Na]. For $C_{12}H_{12}N_4OS$ (260.31) calculated: 55.37% C, 4.65% H, 21.52% N, 12.32% S; found: 55.16% C, 4.66% H, 21.17% N, 12.39% S.

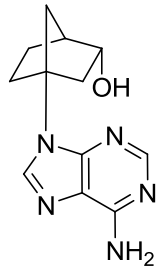


(1*S,2*R**,4*S**)-4-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (346)**

$NaBH_4$ (52 mg, 1.4 mmol) was added portionwise to a solution of **341** (600 mg, 2.3 mmol) in dry methanol (15 mL) at 0°C and the reaction mixture was stirred at this temperature for one hour. A saturated solution of ammonium chloride (30 mL) was added and product was extracted with ethyl acetate (5 x 30 mL). Combined organic extracts were dried over sodium sulfate and chromatographed on silica gel (ethyl acetate - toluene - acetone - ethanol 17:4:3:1) to afford **346** (540 mg, 89%) as white powder. For analytical purposes 100 mg of the product was crystallized from toluene - cyclohexane mixture (m.p. = 154°C, white crystals).

^{1}H NMR (500 MHz, DMSO): 1.65 (m, 1H, H-6exo), 1.80 (dm, 1H, J_{gem} = 12.2, H-3endo), 1.97 (m, 1H, H-5exo), 2.11 – 2.21 (m, 4H, H-5endo, H-6endo, H-7), 2.29 (m, 1H, H-1), 2.31 (ddd, 1H, J_{gem} = 12.3, J_{3ex-2} = 10.4, $J_{3ex-5ex}$ = 3.8, H-3exo), 4.28 (m, 1H, H-2), 4.99 (d, 1H, J_{OH-2} = 4.1, OH), 8.66 (s, 1H, H-8'), 8.76 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 20.81 (C-6), 34.16 (C-5), 40.15 (C-7), 41.00 (C-1), 43.61 (C-3), 66.11 (C-4), 69.74 (C-2), 131.71 (C-5'), 146.37 (C-8'), 149.34 (C-6'), 151.26 (C-2'), 152.32 (C-4'). ESI MS *m/z* (%): 263.2 (100) [M+H]. For $C_{12}H_{13}N_4OCl$

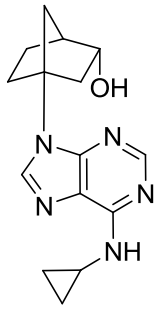
(262.69) calculated: 54.45% C, 4.95% H, 21.17% N, 13.39% Cl; found: 54.28% C, 5.02% H, 21.10% N, 13.39% Cl.



(1*S,2R*,4*S**)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (347)**

Ammonolysis was performed according to method **F1** starting from **346** (110 mg, 0.4 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water. Yield 71 mg, 70%, colorless crystals (m.p. = 252°C).

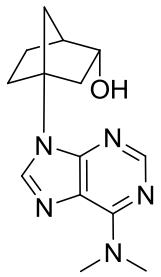
^{1}H NMR (500 MHz, DMSO): 1.61 (m, 1H, H-6exo), 1.73 (dm, 1H, J_{gem} = 12.3, H-3endo), 1.93 (m, 1H, H-5exo), 2.08 - 2.16 (m, 4H, H-5endo, H-6endo, H-7), 2.24 (m, 1H, H-1), 2.58 (ddd, 1H, J_{gem} = 12.3, J_{3ex-2} = 10.5, $J_{3ex-5ex}$ = 3.1, H-3exo), 4.26 (m, 1H, H-2), 4.93 (d, 1H, J_{OH-2} = 4.1, OH), 7.15 (bs, 2H, NH_2), 8.06 (s, 1H, H-8'), 8.11 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 20.84 (C-6), 34.25 (C-5), 40.23 (C-7), 41.07 (C-1), 43.69 (C-3), 65.30 (C-4), 69.89 (C-2), 119.81 (C-5'), 139.50 (C-8'), 150.11 (C-4'), 152.23 (C-2'), 156.28 (C-6'). NegESI MS *m/z* (%): 244.2 (100) [M-H]. For $C_{12}H_{15}N_5O$ (245.28) calculated: 58.76% C, 6.16% H, 28.55% N; found: 58.39% C, 6.25% H, 28.65% N.



(1*S,2*R**,4*S**)-4-[6-(Cyclopropylamino)-9*H*-purin-9-yl]bicyclo [2.2.1]heptan-2-ol (348)**

Nucleophilic displacement performed according to method **G1** starting from **346** (130 mg, 0.5 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 117 mg, 85 %, white crystals (m.p. = 201-202°C).

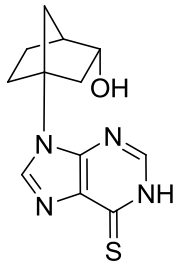
^{1}H NMR (500 MHz, DMSO): 0.59 (m, 2H, CH_2-cyclop), 0.70 (m, 2H, CH_2-cyclop), 1.61 (m, 1H, H-6exo), 1.73 (dm, 1H, J_{gem} = 12.4, H-3endo), 1.93 (m, 1H, H-5exo), 2.08 - 2.16 (m, 4H, H-5endo, H-6endo, H-7), 2.22-2.30 (m, 2H, H-3exo, H-1), 3.00 (bs, 1H, CH-cyclop), 4.25 (m, 1H, H-2), 4.94 (d, 1H, J_{OH-2} = 4.1, OH), 7.85 (bs, 1H, NH), 8.07 (s, 1H, H-8'), 8.22 (bs, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 6.57 (CH_2-cyclop), 20.86 (C-6), 34.27 (C-5), 40.24 (C-7), 41.08 (C-1), 43.71 (C-3), 65.32 (C-4), 69.90 (C-2), 120.21 (C-5'), 139.35 (C-8'), 149.49 (C-4'), 152.15 (C-2'), 155.83 (C-6'). ESI MS *m/z* (%): 286.3 (100) [M+H]. For $C_{15}H_{19}N_5O$ (285.16) calculated: 63.14% C, 6.71% H, 24.54% N; found: 63.12% C, 6.74% H, 24.69% N.



(1*S,2R*,4*S**)-4-[6-(Dimethylamino)-9H-purin-9-yl]bicyclo[2.2.1] heptan-2-ol (349)**

Nucleophilic displacement performed according to method **H2** starting from **346** (110 mg, 0.4 mmol). Mobile phase: ethyl acetate - toluene - acetone - ethanol 17:4:3:1. Crystallization from toluene - cyclohexane mixture. Yield 87 mg, 77 %, white crystals (m.p. = 156°C).

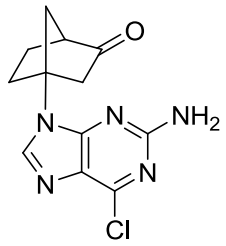
^{1}H NMR (500 MHz, DMSO): 1.60 (m, 1H, H-6exo), 1.74 (dm, 1H, J_{gem} = 12.4, H-3endo), 1.91 (m, 1H, H-5exo), 2.08 - 2.16 (m, 4H, H-5endo, H-6endo, H-7), 2.22 - 2.30 (m, 2H, H-1, H-3exo), 3.44 (bs, 6H, CH_3), 4.25 (m, 1H, H-2), 4.94 (d, 1H, J_{OH-2} = 4.0, OH), 8.07 (s, 1H, H-8'), 8.19 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 20.84 (C-6), 34.15 (C-5), 40.17 (C-7), 41.03 (C-1), 43.61 (C-3), 65.35 (C-4), 69.88 (C-2), 120.38 (C-5'), 138.38 (C-8'), 150.95 (C-4'), 151.55 (C-2'), 154.54 (C-6'). ESI MS *m/z* (%): 274.3 (100) [M+H]. For $C_{14}H_{19}N_5O$ (273.33) calculated: 61.52% C, 7.01% H, 25.62% N; found: 61.75% C, 7.05% H, 25.69% N.



(1*S,2R*,4*S**)-4-(6-Sulfanyl-9*H*-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (350)**

Nucleophilic displacement performed according to method **I** starting from **346** (110 mg, 0.4 mmol). Yield 74 mg, 68%, white powder (m.p. > 320°C (decomp.)).

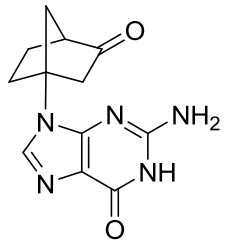
^{1}H NMR (500 MHz, DMSO): 1.62 (m, 1H, H-6exo), 1.75 (m, 1H, J_{gem} = 12.4, H-3endo), 1.90 (m, 1H, H-5exo), 2.07 - 2.16 (m, 4H, H-5endo, H-6endo, H-7), 2.20 - 2.26 (m, 2H, H-1, H-3exo), 4.25 (m, 1H, H-2), 4.97 (bs, 1H, OH), 8.17 (s, 1H, H-2'), 8.23 (s, 1H, H-8'), 13.70 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): 20.88 (C-6), 34.44 (C-5), 40.29 (C-7), 41.02 (C-1), 43.89 (C-3), 65.81 (C-4), 69.80 (C-2), 136.05 (C-5'), 141.90 (C-8'), 144.46 (C-2'), 144.67 (C-4'), 176.07 (C-6'). EI MS *m/z* (%): 262.1 (100) [M]. For $C_{12}H_{14}N_4OS$ (262.33) calculated: 54.94% C, 5.38% H, 21.36% N, 12.22% S; found: 54.61% C, 5.40% H, 21.60% N, 12.26% S.



(1*R,4*R**)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)bicyclo[2.2.1] heptan-2-one (351)**

A solution of **337** (1.11 g, 4 mmol) in DMF (10 mL) was added dropwise to a solution of PDC (3 g, 8 mmol) in DMF (70 mL). Reaction mixture was stirred 12 h at RT, volatiles were evaporated and product was purified by flash chromatography (1-3% methanol in ethyl acetate). Crystallization from toluene afforded **351** (620 mg, 56%) as white crystals (m.p. = 209°C).

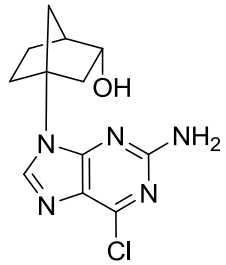
^{1}H NMR (500 MHz, DMSO): δ1.53 (m, 1H, H-6endo), 2.07 (m, 1H, H-6exo), 2.18 - 2.25 (m, 2H, H-5), 2.44 (ddd, 1H, J_{gem} = 9.8, $J_{7b,3en}$ = 3.9, $J_{7b,1}$ = 1.3, H-7b), 2.49 (m, 1H, H-7a), 2.71 - 2.84 (m, 3H, H-1, H-3), 6.90 (bs, 2H, NH_2), 8.19 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ23.27 (C-6), 31.35 (C-5), 39.7 (C-7), 48.25 (C-3), 48.96 (C-1), 62.78 (C-4), 124.17 (C-5'), 141.83 (C-8'), 149.80 (C-6'), 154.50 (C-4'), 159.59 (C-2'), 211.54 (C-2). ESI MS *m/z* (%): 278.1 (43) [M+H], 300.0 (100) [M+Na]; HRMS ESI ($C_{12}H_{13}ON_5Cl$) calculated: 278.08031; found: 278.08041.



2-Amino-9-[(1*R,4*R**)-3-oxobicyclo[2.2.1]hept-1-yl]-1,9-dihydro-6*H*-purin-6-one (352)**

Hydrolysis to guanine derivative was performed according to method **J** starting from **337** (150 mg, 0.54 mmol). Yield 120 mg, 86%, brown powder (m.p. > 360°C (decomp)).

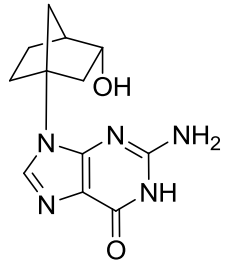
^{1}H NMR (500 MHz, DMSO): δ1.50 (m, 1H, H-5endo), 2.05 (m, 1H, H-5exo), 2.13 - 2.22 (m, 2H, H-6), 2.37 (ddd, 1H, J_{gem} = 9.8, $J_{7b,3en}$ = 4.0, $J_{7b,1}$ = 1.4, H-7b), 2.46 (dm, 1H, J_{gem} = 9.8, H-7a), 2.68 (m, 1H, H-4), 2.69 (dd, 1H, J_{gem} = 17.2, $J_{2en,7b}$ = 4.0, H-2endo), 2.77 (dm, 1H, J_{gem} = 17.2, H-2exo), 6.39 (bs, 2H, NH_2), 7.74 (s, 1H, H-8'), 10.61 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ23.37 (C-5), 31.55 (C-6), 39.8 (C-7), 48.48 (C-2), 49.00 (C-4), 62.54 (C-1), 117.71 (C-5'), 135.95 (C-8'), 151.76 (C-4'), 153.16 (C-2'), 156.99 (C-6'), 211.90 (C-3). ESI MS *m/z* (%): 260.2 (40) [M+H], 282.2 (100) [M+Na]; HRMS ESI ($C_{12}H_{13}O_2N_5Na$) calculated: 282.09615; found: 282.09613. For $C_{12}H_{13}N_5O_2$. 0.5 H_2O (268.27) calculated: 53.72% C, 5.26% H, 26.11% N; found: 53.65% C, 5.19% H, 25.96% N.



(1*R,2*S**,4*R**)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)bicyclo [2.2.1]heptan-2-ol (353)**

$NaBH_4$ (39 mg, 1 mmol) was added portionwise to a solution of **351** (470 mg, 1.7 mmol) in dry methanol (30 mL) at 0°C and the reaction mixture was stirred at this temperature for 5 hours. A saturated solution of ammonium chloride (30 mL) and water (100 mL) were added and product was extracted into ethyl acetate (5 x 50 mL). Organic extracts were combined and dried with sodium sulfate. Flash chromatography (1-10% methanol in ethyl acetate) and crystallization from toluene - ethyl acetate mixture afforded **353** (430 mg, 51%) as white powder (m.p. = 213°C).

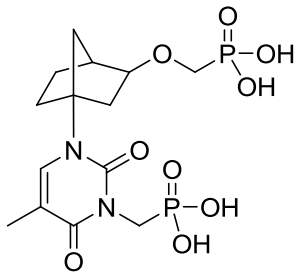
^{1}H NMR (500 MHz, DMSO): δ 1.59 (m, 1H, H-6exo), 1.74 (dm, 1H, J_{gem} = 12.3, H-3endo), 1.89 (m, 1H, H-5exo), 2.07 - 2.15 (m, 4H, H-5endo, H-6endo, H-7), 2.21 (ddd, 1H, J_{gem} = 12.3, $J_{3ex,2}$ = 10.4, $J_{3ex,5ex}$ = 3.7, H-3exo), 2.23 (m, 1H, H-1), 4.24 (m, 1H, H-2), 4.93 (d, 1H, J_{OH-2} = 3.9, OH), 6.81 (bs, 2H, NH_2), 8.06 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.74 (C-6), 33.91 (C-5), 40.00 (C-7), 40.93 (C-1), 43.37 (C-3), 65.33 (C-4), 69.76 (C-2), 124.25 (C-5'), 141.98 (C-8'), 149.60 (C-6'), 154.53 (C-4'), 159.46 (C-2'). ESI MS *m/z* (%): 280.1 (73) [M+H], 302.1 (100) [M+Na]; HRMS ESI ($C_{12}H_{14}ON_5ClNa$) calculated: 302.07791; found: 302.07789.



2-Amino-9-[(1*R,3*R**,4*R**)-3-hydroxybicyclo[2.2.1]hept-1-yl]-1,9-dihydro-6*H*-purin-6-one (354)**

Hydrolysis to guanine derivative was performed according to method **J** starting from **353** (100 mg, 0.36 mmol). Yield 60 mg, 64%, pale orange powder (m.p. > 360°C (decomp)).

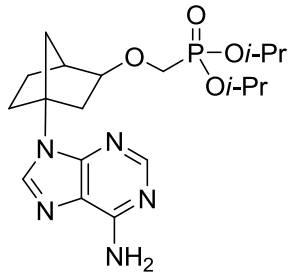
^{1}H NMR (500 MHz, DMSO): δ 1.56 (m, 1H, H-6exo), 1.70 (dm, 1H, J_{gem} = 12.5, H-3endo), 1.82 (m, 1H, H-5exo), 2.02 - 2.18 (m, 4H, H-5endo, H-6endo, H-7), 2.15 (m, 1H, H-3exo), 2.19 (m, 1H, H-1), 4.21 (m, 1H, H-2), 4.88 (d, 1H, J_{OH-2} = 3.7, OH), 6.30 (bs, 2H, NH_2), 7.60 (s, 1H, H-8'), 10.52 (bs, 1H, H-1'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.71 (C-6), 33.80 (C-5), 40.05 (C-7), 40.88 (C-1), 42.80 (C-3), 66.48 (C-4), 69.91 (C-2), 117.45 (C-5'), 133.01 (C-8'), 152.44 (C-4'), 153.88 (C-2'), 155.13 (C-6'). ESI MS *m/z* (%): 262.2 (61) [M+H], 284.2 (100) [M+Na]; HRMS ESI ($C_{12}H_{16}O_2N_5$) calculated: 262.12985, found: 262.12988. For $C_{12}H_{15}N_5O_2$ (261.28) calculated: 55.16% C, 5.79% H, 26.80% N; found: 55.32% C, 5.85% H, 26.50% N.



({5-methyl-2,6-Dioxo-3-[(1*R,3*R**,4*R**)-3-(phosphonomethoxy)bicyclo[2.2.1]hept-1-yl]-3,6-dihydropyrimidin-1(2*H*)-yl}methyl)phosphonic acid (355)**

Preparation of bisphosphonate tetraester was performed according to method **K1** starting from **331** (100 mg, 0.42 mmol). Mobile phase: 1-2% methanol in ethyl acetate. Subsequent transformation to free phosphonate was performed according to method **K2**, Mobile phase: 30-80% methanol in water, C18 column. Yield 107 mg, 60%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, D_2O): δ 1.34 (m, 1H, H-5endo), 1.57 - 1.66 (m, 2H, H-2exo, H-6exo), 1.82 - 1.91 (m, 2H, H-5exo, H-7b), 1.90 (d, 3H, $J_{CH3,6'}$ = 1.1, CH_3), 2.13 - 2.24 (m, 2H, H-6endo, H-7a), 2.71 (ddd, 1H, J_{gem} = 13.0, $J_{2en,3}$ = 6.9, $J_{2en,7b}$ = 2.4, H-2endo), 3.68 (dd, 1H, J_{gem} = 13.7, $J_{H,C,P}$ = 9.3, OCH_2Pb), 3.73 (dd, 1H, J_{gem} = 13.7, $J_{H,C,P}$ = 9.1, OCH_2Pa), 3.82 (m, 1H, H-3), 4.33 (d, 2H, $J_{H,C,P}$ = 12.4, NCH_2Pb), 7.61 (bs, 1H, H-6'). ^{13}C NMR (125.8 MHz, D_2O): δ 12.72 (CH_3), 24.36 (C-5), 31.59 (C-6), 38.69 (C-7), 39.02 (d, J_{C-P} = 149.4, NCH_2-P), 42.02 (C-2), 63.63 (d, J_{C-P} = 159.8, OCH_2-P), 71.44 (C-1), 84.79 (d, J_{2-P} = 11.6, C-3), 108.96 (C-5'), 140.35 (C-6'), 152.18 (C-2'), 165.68 (C-4'). NegESI MS *m/z* (%): 423.1 (100) [M-H]; HRMS negESI ($C_{14}H_{21}O_9N_2P_2$) calculated: 423.07278; found: 423.07269. For $C_{14}H_{22}N_2O_9P_2$ (424.28) calculated: 39.63% C, 5.23% H, 6.60% N; 14.60% P; found: 39.81% C, 5.21% H, 6.40% N, 14.52% P.

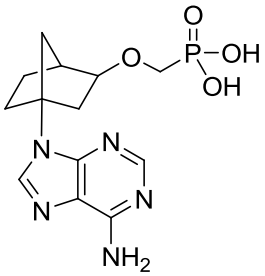


Diisopropyl [({4-[6-amino-9*H*-purin-9-yl]bicyclo[2.2.1]hept-2-yl}oxy)methyl]phosphonate (356)

Preparation of phosphonate diester was performed according to method **K1** starting from **333** (231 mg, 0.94 mmol). Mobile phase: 3-10% methanol in ethyl acetate. Yield 350 mg, 89%, clear oil.

^{1}H NMR: δ 1.24 (m, 12H, CH_3-*i*-Pr); 1.30 (m, 1H, H-6endo), 1.81 (m, 1H, H-6exo), 1.84 (m, 1H, H-3exo), 1.91 (m, 1H, H-5exo), 1.97 (m, 1H, H-5endo); 2.03 (dm, 1H, J_{gem} = 9.4, H-7b), 2.28 (dm, 1H, J_{gem} = 9.4, H-7a), 2.5 (m, 2H, H-1, H-3endo), 3.68 - 3.79 (m, 3H, CH_2P, H-2), 4.60 (m, 2H, CH-*i*-Pr), 7.18 (s, 2H, NH_2), 8.11 (s, 1H, H-2'), 8.14 (s, 1H, H-8'). ^{13}C NMR: δ 23.87 (C-6), 23.89 - 24.06 (m,

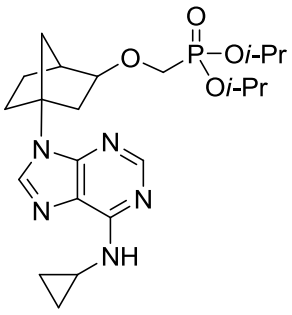
CH_3-*i*-Pr), 32.61 (C-5), 37.83 (C-7), 38.61 (C-1), 43.11 (C-3), 62.54 (d, J_{C-P} = 165.7, CH_2-P), 64.15 (C-4), 70.35 (d, J_{C-P} = 6.2, *CH*-*i*-Pr), 83.40 (d, J_{2-P} = 13.1, C-2), 119.79 (C-5'), 139.70 (C-8'), 150.19 (C-4'), 152.26 (C-2'), 156.30 (C-6'). ESI MS *m/z* (%): 424.3 (100) [M+H], 446.3 (95) [M+Na]; HRMS ESI ($C_{19}H_{30}O_4N_5NaP$) calculated: 446.19276; found: 446.19254. For $C_{19}H_{30}N_5O_4P$ (423.45) calculated: 53.89% C, 7.14% H, 16.54% N; 7.31% P; found: 53.94% C, 7.23% H, 16.15% N, 7.38% N.



[({4-[6-Amino-9*H*-purin-9-yl]bicyclo[2.2.1]hept-2-yl}oxy) methyl]phosphonic acid (357)

Preparation of free phosphonate was performed according to method **K2** starting from **356** (250 mg, 0.59 mmol). Yield 190 mg, 95%, white poorly soluble powder (m.p. = 289 - 290°C).

^{1}H NMR (500 MHz, D_2O): δ 1.42 (m, 1H, H-6endo), 1.82 (m, 1H, H-5exo), 1.87 - 1.94 (m, 2H, H-3exo, H-6exo), 1.97 - 2.03 (m, 2H, H-5endo, H-7b), 2.38 (dm, 1H, J_{gem} = 9.1, H-7a), 2.55 (m, 1H, H-3endo), 2.60 (bd, 1H, $J_{1,6ex}$ = 5.0, H-1), 3.43 (dd, 1H, J_{gem} = 12.5, $J_{H,C,P}$ = 9.3, CH_2Pb), 3.49 (dd, 1H, J_{gem} = 12.5, $J_{H,C,P}$ = 9.0, CH_2Pa), 3.87 (m, 1H, H-2), 8.12 - 8.14 (m, 2H, H-2', H-8'). ^{13}C NMR (125.8 MHz, D_2O): δ 24.52 (C-6), 32.90 (C-5), 38.51 (C-7), 39.33 (C-1), 43.30 (C-3), 65.44 (C-4), 66.65 (d, J_{C-P} = 151.0, CH_2-P), 83.98 (d, J_{2-P} = 11.0, C-2), 119.87 (C-5'), 141.95 (C-8'), 149.86 (C-4'), 152.38 (C-2'), 156.05 (C-6'). NegESI MS *m/z* (%): 338.1 (100) [M-H]; HRMS negESI ($C_{13}H_{17}O_4N_5P$) calculated: 338.10236; found: 338.10268. For $C_{13}H_{18}N_5O_4P$ (339.29) calculated: 46.02% C, 5.35% H, 20.64% N; 9.13% P; found: 46.37% C, 5.21% H, 20.29% N, 9.02% P.

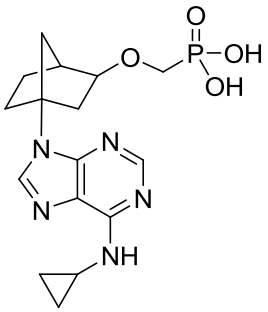


Diisopropyl [({4-[6-(cyclopropylamino)-9*H*-purin-9-yl] bicyclo[2.2.1]hept-2-yl}oxy)methyl]phosphonate (358)

Preparation of phosphonate diester was performed according to method **K1** starting from **334** (280 mg, 0.8 mmol). Mobile phase: 1-3% methanol in ethyl acetate. Yield 70 mg, 25%, clear oil.

^{1}H NMR (500 MHz, DMSO): 0.66 and 0.92 (m, 4H, CH_2-cyklop), 1.32-1.34 (m, 12H, CH_3-*i*Pr), 1.90 – 1.98 (m, 4H, H-3exo, H-5a, H-6), 2.09 - 2.16 (m, 2H, H-5b, H-7a), 2.40 (dm, 1H, J_{gem} = 9.2, H-7b), 2.57 (m, 1H, H-1), 2.69 (ddd, 1H, J_{gem} =

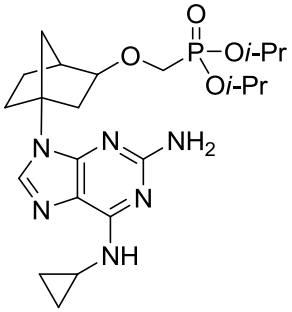
12.8, J_{3en-2} = 6.9, J_{3en-7a} = 2.6, H-3endo), 3.02 (bs, 1H, CH-cyklop), 3.69 (dd, 1H, J_{gem} = 13.4 J_{H-C-P} = 9.5) and 3.74 (dd, 1H, J_{gem} = 13.4, J_{H-C-P} = 9.4, CH_2P), 3.79 (dm, 1H, J_{2-3en} = 7.0, H-2), 4.71 – 4.80 (m, 2H, CH-*i*Pr), 6.04 (bs, 1H, NH), 7.76 (s, 1H, H-8'), 8.46 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 7.31 (CH_2-cyklop), 23.98-24.09 (CH_3-*i*Pr), 24.20 (C-6), 33.02 (C-5), 38.16 (C-7), 38.90 (C-1), 43.35 (C-3), 63.26 (d, J_{C-P} = 169.8, CH_2P), 64.49 (C-4), 71.07 (d, J_{C-O-P} = 6.7, CH-iPr), 83.90 (d, J_{3-P} = 12.7, C-2), 120.70 (C-5'), 138.35 (C-8'), 149.90 (C-4'), 152.64 (C-2'), 155.74 (C-6'). HRMS ESI ($C_{22}H_{35}N_5O_4P$) calculated: 464.2421, found: 464.2420.



[({4-[6-(Cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.1] hept-2-yl}oxy)methyl]phosphonic acid (359)

Preparation of free phosphonate was performed according to method **K2** starting from **358** (70 mg, 0.15 mmol). Yield 53 mg, 92%, white solid.

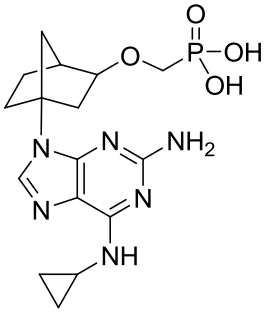
^{1}H NMR (500 MHz, D_2O): 0.90 and 1.12 (m, 4H, CH_2-cyklop), 1.62 (m, 1H, H-6endo), 1.94 – 2.01 (m, 3H, H-3exo, H-5endo, H-6exo), 2.11 - 2.16 (m, 2H, H-5exo, H-7a), 2.47 (dm, 1H, J_{gem} = 9.6, H-7b), 2.65 (m, 1H, H-1), 2.68 (ddd, 1H, J_{gem} = 12.7, J_{3en-2} = 6.8, J_{3en-7a} = 2.5, H-3endo), 2.91 (bs, 1H, CH-cyklop), 3.73 (dd, 1H, J_{gem} = 13.7, J_{H-C-P} = 9.4, CH_2Pa), 3.80 (dd, 1H, J_{gem} = 13.7, J_{H-C-P} = 9.1, CH_2Pb), 3.94 (dm, 1H, J_{2-3en} = 6.8, H-2), 8.36 (s, 1H, H-8'), 8.43 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, D_2O): 7.31 (CH_2-cyklop), 23.33 (CH-cyklop), 24.25 (C-4), 33.15 (C-5), 38.43 (C-7), 39.45 (C-1), 43.41 (C-3), 63.93 (d, J_{C-P} = 159.9, (CH_2P), 66.14 (C-4), 71.07 (d, J_{C-O-P} = 6.7, CH-*i*Pr), 83.90 (d, J_{3-P} = 12.7, C-3), 120.70 (C-5'), 138.35 (C-8'), 149.90 (C-4'), 152.64 (C-2'), 155.74 (C-6'). HRMS ESI ($C_{16}H_{22}N_5O_4P$) calculated: 380.1482, found: 380.1482.



Diisopropyl [({4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.1]hept-2-yl}oxy)methyl] phosphonate (360)

Preparation of phosphonate diester was performed according to method **K1** starting from **339** (250 mg, 0.83 mmol). Mobile phase: 1-2% methanol in ethyl acetate. Yield 320 mg, 81%, clear oil.

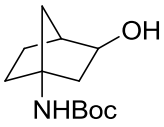
^{1}H NMR (500 MHz, DMSO): δ 0.57 and 0.65 (m, 4H, CH_2-cyclop), 1.22 - 1.26 (m, 12H, *CH_3*-*i*-Pr), 1.26 (m, 1H, H-6endo), 1.71 (dm, 1H, J_{gem} = 12.8, H-3exo), 1.75 - 1.85 (m, 2H, H-5exo, H-6exo), 1.93 (m, 1H, H-5endo), 2.07 (dm, 1H, J_{gem} = 9.4, H-7b), 2.12 (dm, 1H, J_{gem} = 9.4, H-7a), 2.45 (m, 1H, H-1), 2.54 (ddd, 1H, J_{gem} = 12.8, $J_{3en,2}$ = 6.8, $J_{3en,7}$ = 2.2, H-3endo), 3.01 (bs, 1H, CH-cyclop), 3.69 (dd, 1H, J_{gem} = 13.7, $J_{H,C,P}$ = 9.2, CH_2Pa), 3.72 (m, 1H, H-2), 3.75 (dd, 1H, J_{gem} = 13.7, $J_{H,C,P}$ = 8.9, CH_2Pb), 4.55 - 4.64 (m, 2H, *CH*-*i*-Pr), 5.69 (bs, 2H, NH_2), 7.25 (m, 1H, NH), 7.69 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 6.58 (CH_2-cyclop), 23.88 - 24.04 (m, *CH_3*-*i*-Pr), 23.99 (C-6), 32.43 (C-5), 37.75 (C-7), 38.60 (C-1), 43.07 (C-3), 62.51 (d, J_{C-P} = 165.8, CH_2-P), 63.62 (C-4), 70.28 (m, *CH*-*i*-Pr), 83.37 (d, J_{2-P} = 13.0, C-2), 114.52 (C-5'), 135.91 (C-8'), 152.0 (C-4'), 156.11 (C-6'), 159.87 (C-2'). NegESI MS *m/z* (%): 423.1 (100) [M-H]; HRMS negESI ($C_{14}H_{21}O_9N_2P_2$) calculated: 423.07278; found: 423.07269. For $C_{22}H_{35}N_6O_4P$ (478.52) calculated: 55.22% C, 7.37% H, 17.56% N; 6.47% P; found: 55.28% C, 7.47% H, 17.30% N, 6.78% P.



[({4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]bicyclo [2.2.1]hept-2-yl}oxy)methyl]phosphonic acid (361)

Preparation of free phosphonate was performed according to method **K2** starting from **360** (220 mg, 0.46 mmol). Mobile phase: (30-80% methanol in water). Yield 164 mg, 90%, clear solid or white lyophilizate.

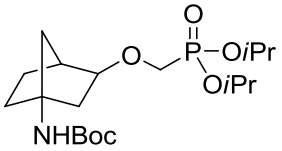
^{1}H NMR (500 MHz, D_2O): δ 0.83 and 1.05 (m, 4H, CH_2-cyclop), 1.36 (m, 1H, H-6endo), 1.79 - 1.98 (m, 5H, H-5, H-3exo, H-6exo, H-7b), 2.30 (dm, 1H, J_{gem} = 9.4, H-7a), 2.54 (ddd, 1H, J_{gem} = 12.6, $J_{3en,2}$ = 6.9, $J_{3en,7b}$ = 2.3, H-3endo), 2.56 (bd, 1H, $J_{1,6ex}$ = 4.8, H-1), 2.84 (bs, 1H, CH-cyclop), 3.59 (dd, 1H, J_{gem} = 13.3, $J_{H,C,P}$ = 9.5, CH_2Pb), 3.67 (dd, 1H, J_{gem} = 13.3, $J_{H,C,P}$ = 9.0, CH_2Pa), 3.83 (m, 1H, H-2), 7.92 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, D_2O): δ 7.53 (CH_2-cyclop), 24.14 (C-6), 32.85 (C-5), 38.13 (C-7), 39.19 (C-1), 43.02 (C-3), 64.81 (d, J_{C-P} = 156.9, CH_2-P), 65.43 (C-4), 84.36 (d, J_{2-P} = 11.9, C-2), 112.50 (C-5'), 141.51 (C-8'), 151.4 (C-4'), 150.63 and 152.47 (C-2', C-6'). NegESI MS *m/z* (%): 393.1 (100) [M-H]; HRMS negESI ($C_{16}H_{22}O_4N_6P$) calculated: 393.14456; found: 393.14462. For $C_{16}H_{23}N_6O_4P$ (394.37) calculated: 48.73% C, 5.88% H, 21.31% N; 7.85% P; found: 48.91% C, 5.76% H, 21.33% N, 7.72% P.



Tert-butyl [(1*R,3*R**,4*R**)-3-hydroxybicyclo[2.2.1]hept-1-yl]carbamate (362)**

To a solution of **330** (655 mg, 4 mmol) and DIPEA (2.09 mL, 12 mmol) in DCM (25 mL) was added Boc-anhydride (1.31 g, 6 mmol) and the reaction mixture was stirred at RT overnight. DCM was evaporated and the resulting slurry was dissolved in ethyl acetate and washed with water (2 x 50 mL). Organic layer was dried over sodium sulfate, evaporated and the crude product was purified by flash chromatography (30-50% ethyl acetate in hexane) and crystallized hrom hexane to afford **361** (807 mg, 89%) as white crystals.

^{1}H NMR (500 MHz, DMSO): δ 1.12 (m, 1H, H-5endo), 1.34 - 1.40 (m, 2H, H-6endo, H-7b), 1.40 (s, 9H, CH_3), 1.47 (dm, 1H, J_{gem} = 12.5, H-2exo), 1.52 - 1.61 (m, 2H, H-5exo, H-6exo), 1.84 (dm, 1H, J_{gem} = 9.1, H-7a), 1.89 - 1.92 (m, 2H, H-4, H-2endo), 3.66 (dm, 1H, $J_{3,2en}$ = 7.0, H-3), 6.46 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 24.07 (C-5), 28.09 (CH_3), 31.99 (C-6), 37.39 (C-7), 42.17 (C-4), 45.80 (C-2), 59.99 (C-1), 72.77 (C-3), 77.03 (CH_3), 154.51 (COO). ESI MS *m/z* (%): 250.1 (100) [M+Na]; HRMS ESI ($C_{12}H_{21}O_3NNa$) calculated: 250.14136; found: 250.14125. For $C_{12}H_{21}NO_3$ (227.30) calculated: 63.41% C, 9.31% H, 6.16% N; found: 63.43% C, 9.33% H, 6.23% N.

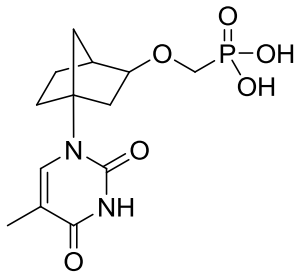


Diisopropyl [({(1*R,3*R**,4*R**)-4-[(*tert*-butoxycarbonyl) amino]bicyclo[2.2.1]hept-2-yl}oxy)methyl]phosphonate (363)**

Preparation of phosphonate diester was performed according to method **K1** starting from **362** (770 mg, 3.39 mmol). Mobile phase: 60-100% ethyl acetate in hexane. Yield 800 mg, 58%, clear oil.

^{1}H NMR (500 MHz, DMSO): δ 1.09 (m, 1H, H-6endo), 1.22 - 1.25 (m, 12H, **CH$_3$**CH), 1.37 (s, 9H, **CH$_3$**C), 1.33 - 1.40 (m, 2H, H-5endo, H-7b), 1.50 - 1.62 (m, 3H, H-3exo, H-6exo, H-5exo), 1.67 (m, 1H, H-7a), 1.88 (m, 1H, H-3endo), 2.20 (m, 1H, H-1), 3.51 (m, 1H, H-2), 3.60 (dd, 1H, J_{gem} = 13.7, $J_{H,C,P}$ = 9.3, CH_2Pb), 3.68 (dd, 1H, J_{gem} = 13.7, $J_{H,C,P}$ = 9.0, CH_2Pa), 4.54 - 4.63 (m, 2H, CH_3**CH**), 7.03 and 7.32 (bs, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ 23.87 - 24.05 (m, **CH$_3$**CH), 24.06 (C-6), 28.46 (**CH$_3$**C), 32.07 (C-5), 37.83 (C-7), 38.13 (C-1), 42.74 (C-3), 60.09 (C-4), 62.48 (d, J_{C-P} = 166.0, CH_2-P), 70.21 - 70.29 (m, CH_3**CH**), 77.48 (CH_3**C**), 83.89

(d, $J_{2\text{-}P}$ = 13.3, C-2), 154.80 and 154.97 (COO). ESI MS *m/z* (%): 406.3 (17) [M+H], 428.3 (100) [M+Na]; HRMS ESI ($C_{19}H_{36}O_6NNaP$) calculated: 428.21725; found: 428.21728.



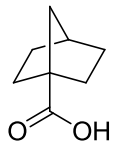
({[(1*R,3*R**,4*R**)-4-(5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl)bicyclo[2.2.1]hept-2-yl]oxy}methyl) phosphonic acid (365)**

To a solution **363** in DCM (10 mL) was added TFA (2 mL) and the reaction mixture was stirred at RT for 2 h. Volatiles were evaporated and product was codistiled with dry ethanol (3 x 15 mL), purified on Dowex 50 (H^+) to afford **364** (320 mg, 56%) as brownish oil, which was directly used in the next reaction.

Thymine nucleobase construction was performed according to method **E** starting from **364** (280 mg, 0.92 mmol). Mobile phase: 30-80% methanol in water (C-18 column). Yield 130 mg, 43%, clear solid or white lyophilizate.

^{1}H NMR (500 MHz, D_2O): δ 1.21 (m, 1H, H-6endo), 1.41 - 1.51 (m, 2H, H-3exo, H-5exo), 1.77 (d, 3H, CH_3), 1.69 - 1.80 (m, 2H, H-6exo, H-7b), 2.02 - 2.11 (m, 2H, H-5exo, H-7a), 2.34 (d, 1H, $J_{1,6ex}$ = 5.2, H-1), 2.59 (ddd, 1H, J_{gem} = 12.9, $J_{3en,2}$ = 2.1, $J_{3en,7a}$ = 2.1, H-3endo), 3.44 (dd, 1H, J_{gem} = 13.2, $J_{H,C,P}$ = 9.6, CH_2Pb), 3.49 (dd, 1H, J_{gem} = 13.2, $J_{H,C,P}$ = 9.7, CH_2Pa), 3.63 (d, 1H, $J_{2,3en}$ = 6.6, H-2), 4.67 (bs, 2H, POH), 7.50 (d, 1H, $J_{6',CH3}$ = 1.1, H-6'), 11.11 (s, 1H, NH). ^{13}C NMR (125.8 MHz, D_2O): δ 12.18 (CH_3), 23.99 (C-6), 31.47 (C-5), 37.46 (C-1), 38.31 (C-7), 42.19 (C-3), 63.96 (d, $J_{C\text{-}P}$ = 162.5, CH_2-P), 68.78 (C-4), 83.06 (d, $J_{2\text{-}P}$ = 12.4, C-2), 107.93 (C-5'), 139.92 (C-6'), 151.09 (C-2'), 164.31 (C-4'). NegESI MS *m/z* (%): 329.2 (100) [M-H]; HRMS NegESI ($C_{13}H_{18}O_6N_2P$) calculated: 329.08970; found: 329.08997.

5.8. Synthesis of N-9 alkylated 6-chloropurines and related compounds

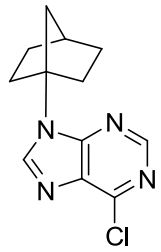


Bicyclo[2.2.1]heptane-1-carboxylic acid (366)

Mixture of **274** (2 g, 9 mmol), NaOH (1.2 g, 30 mmol) and $Pd(OH)_2/C$ (200 mg) in 20 mL of methanol - water mixture (3:1, *v/v*) was treated with 5 atm of hydrogen overnight. The reaction mixture was acidified (pH=5) using 2M HCl and all solids were filtered off on a cellite pad. Filtrate was diluted with water (50 mL), methanol was evaporated and product was extracted with ethyl acetate (3 x 30 mL). Organic extracts were dried over sodium sulfate and evaporated. Sublimation of the crude product (100°C, 3 mbar) afforded **366** (930 mg, 75 %) as white solid. Spectral characteristics match those described in literature.[150]

Bicyclo[2.2.1]heptan-1-amine hydrochloride (367)

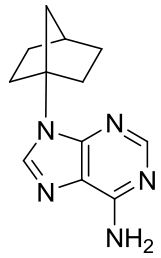
Curtius rearrangement was performed according to **Method D** starting from **366** (670 mg, 4.9 mmol). Yield 359 mg, 50%, brownish oil (purity >96% on LC-MS), used for subsequent reactions without further purification. Spectral characteristics match those described in literature.[149]



9-(Bicyclo[2.2.1]hept-1-yl)-6-chloro-9H-purine (368)

6-Chloropurine nucleobase was constructed according to method **C1** (730 mg, 5 mmol of **367**, EtOH as a solvent, 105°C for 6d in sealed vessel). Mobile phase toluene - ethyl acetate 10:1. Crystallization from water - methanol mixture. Yield 615 mg, 61% as white crystals (m.p. = 129°C).

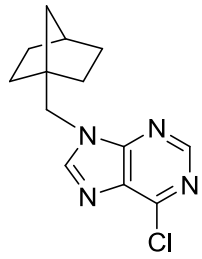
^{1}H NMR (500 MHz, $CDCl_3$): 1.63 (m, 2H, H-3'endo,H-5'endo), 1.99 (m, 2H, H-3'exo,H-5'exo), 2.07 (m, 2H, H-2'exo, H-6'exo), 2.22 (m, 2H, H-7'), 2.26 (m, 2H, H-2'endo, H-6'endo), 2.48 (m, 1H, H-4'), 8.15 (s, 1H, H-8), 8.73 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 29.80 (C-3', C-5'), 34.26 (C-2', C-6'), 35.29 (C-4'), 41.77 (C-7'), 67.00 (C-1'), 132.36 (C-5), 144.05 (C-8), 150.95 (C-6), 151.28 (C-2), 152.38 (C-4). ESI MS *m/z* (%): 249 (100) [M+H], 271 (40) [M+Na]. For $C_{12}H_{13}N_4Cl$ (248.71) calculated: 57.95% C, 5.27% H, 22.53% N; 14.25% Cl; found: 57.69% C, 5.31% H, 22.27% N, 14.48% Cl.



9-(Bicyclo[2.2.1]hept-1-yl)-9H-purin-6-amine (369)

Ammonolysis was performed according to method **F2** starting from **368** (125 mg, 0.5 mmol). Mobile phase: 2-6% methanol in ethyl acetate. Crystallization from water - methanol mixture. Yield 95 mg, 83%, white needles (m.p. = 240°C).

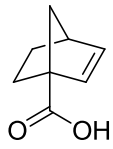
^{1}H NMR (500 MHz, DMSO): 1.49 (m, 2H, H-3'endo,H-5'endo), 1.84 (m, 2H, H-3'exo,H-5'exo), 1.97 (m, 2H, H-2'exo, H-6'exo), 2.08 - 2.14 (m, 4H, H-2'endo, H-6'endo, H-7'), 2.32 (m, 1H, H-4'), 7.15 (bs, 2H, NH_2), 8.10 (s, 1H, H-8), 8.12 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): 29.61 (C-3', C-5'), 33.88 (C-2', C-6'), 34.92 (C-4'), 41.39 (C-7'), 65.81 (C-1'), 119.85 (C-5), 139.72 (C-8), 150.23 (C-6), 152.18 (C-2), 156.28 (C-4). ESI MS *m/z* (%): 230.3 (100) [M+H], 252.3 (18) [M+Na]; HRMS ESI ($C_{12}H_{16}N_5$) calculated: 230.14002, found: 230.13991. For $C_{12}H_{15}N_5$ (229.27) calculated: 62.86% C, 6.59% H, 30.54% N; found: 62.54% C, 6.49% H, 30.19% N.



9-(Bicyclo[2.2.1]hept-1-ylmethyl)-6-chloro-9H-purine (371)

To a solution of **370**[134] (200 mg, 1.6 mmol), PPh_3 (830 mg, 3.2 mmol) and 6-chloropurine (370 mg, 2.4 mmol) in dry THF (20 mL) a solution of DIAD in dry THF (5 mL) was added dropwise, and the reaction mixture was stirred at RT overnight. Volatiles were evaporated and the product was purified by chromatography on silica gel (toluene - ethyl acetate 6:1). Crystallization from water - methanol mixture (95:5) afforded **371** (340 mg, 78%) as white flakes (m.p. = 88°C).

^{1}H NMR (500 MHz, $CDCl_3$): 1.26 (m, 2H, H-7'), 1.24-1.37 (m, 4H, H-2'endo, H-3'endo, H-5'endo, H-6'endo), 1.48 (m, 2H, H-2'exo, H-6'exo), 1.64 (m, 2H, H-3'exo, H-5'exo), 2.26 (m, 1H, H-4'), 4.49 (s, 2H, CH_2N), 8.11 (s, 1H, H-8), 8.75 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 30.22 (C-3', C-5'), 32.96 (C-2', C-6'), 37.11 (C-4'), 42.11 (C-7'), 49.02 (CH_2N), 49.21 (C-1'), 131.15 (C-5), 145.80 (C-8), 150.98 (C-$_6$), 151.88 (C-2), 152.26 (C-4). ESI MS *m/z* (%): 263 (100) [M+H]. For $C_{13}H_{15}N_4Cl$ (262.74) calculated: 59.43% C, 5.75% H, 21.32% N; 13.49% Cl; found: 59.44% C, 5.78% H, 21.00% N, 13.15% Cl.

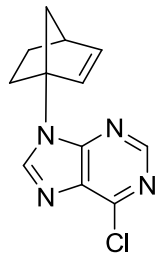


Bicyclo[2.2.1]hept-2-en-1-carboxylic acid (372)

A solution of NaOH (1 g) in water (10 mL) was added to a solution of **277** (1g, 6.6 mmol) in methanol (20 mL) and the reaction mixture was refluxed for 1h. Methanol was evaporated and the residue was diluted with water, washed with Et_2O (2 x 30 mL), acidified with 2M HCl to pH = 3 and extracted with Et_2O (3 x 50 mL). Combined organic layers were dried with Na_2SO_4 and evaporated to afford **372** (870 mg, 95 %, >97% pure on GC-MS analysis). Spectral characteristics match those described in literature.[150]

Bicyclo[2.2.1]hept-2-en-1-amine hydrochloride (373)

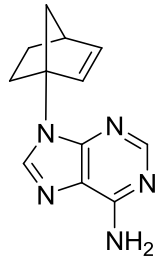
Curtius rearrangement was performed according to **Method D** starting from **372** (870 mg, 6.3 mmol). Yield 750 mg, 79%, white solid of HPLC-MS purity > 95%, used for subsequent reactions without further purification. Analytical sample was crystallized from ethanol - diethylether mixture. Spectral characteristics match those described in literature.[150]



9-(Bicyclo[2.2.1]hept-2-en-1-yl)-6-chloro-9H-purine (374)

6-Chloropurine nucleobase was constructed according to method **C1** (730 mg, 5 mmol of **373**, EtOH as a solvent, 105°C for 7d in sealed vessel). Mobile phase toluene - ethyl acetate 10:1. Crystallization from water - methanol mixture. Yield 490 mg, 40% as white flakes (m.p. = 93°C).

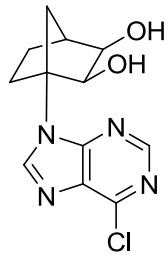
^{1}H NMR (500 MHz, DMSO): 1.43 (bddd, 1H, J_{gem} = 11.6, $J_{5'en-6'en}$ = 9.0, $J_{5'en-6'ex}$ = 4.0, $J_{5'en-7'}$ = 2.4, H-5'endo), 2.0 (dm, 1H, J_{gem} = 7.6, H-7'b), 2.05 (dddd, 1H, J_{gem} = 10.8, $J_{6'en-5'en}$ = 9.0, $J_{6'en-5'ex}$ = 3.8, $J_{6'en-7'}$ = 2.0, H-6'endo), 2.13 (m, 1H, H-5'exo), 2.26 – 2.31 (m, 2H, H-7'a, H-6'exo), 3.13 (m, 1H, H-4'), 6.36 (bdd, 1H, $J_{3'-2'}$ = 5.7, $J_{3'-4'}$ = 3.3, H-3'), 6.42 (bd, 1H, $J_{2'-3'}$ = 5.7, H-2'), 8.24 (s, 1H, H-2), 8.76 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): 26.71 (C-5'), 29.91 (C-6'), 38.39 (C-4'), 52.34 (C-7'), 71.20 (C-1'), 132.38 (C-5), 133.71 (C-2'), 137.10 (C-3'), 143.85 (C-8), 151.07 (C-6), 151.55 (C-2), 152.40 (C-4). ESI MS *m/z* (%): 247.2 (100) [M+H]. For $C_{12}H_{11}N_4Cl \cdot 0{,}25H_2O$ (251.21) calculated: 57.38% C, 4.61% H, 22.30% N, 14.11% Cl; found: 57.60% C, 4.57% H, 22.15% N, 14.32% Cl.



9-[(1R*,4R*)-Bicyclo[2.2.1]hept-2-en-1-yl]-9H-purin-6-amine (375)

Ammonolysis was performed according to method **F2** starting from **374** (100 mg, 0.41 mmol). Mobile phase: 2-6 % methanol in ethyl acetate. Crystallization from water - methanol mixture. Yield 70 mg, 76%, white flakes (m.p. = 224°C).

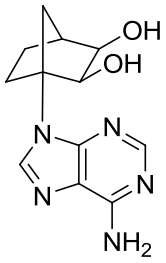
^{1}H NMR (500 MHz, DMSO): 1.24 (m, 1H, H-5'endo), 1.81 (m, 1H, H-6'exo), 2.13 (m, 1H, H-5'exo), 1.98 – 2.06 (m, 3H, H-5'exo, H-7), 2.21 (m, 1H, H-6'endo), 2.99 (m, 1H, H-4'), 6.28 (dd, 1H, $J_{3'-2'}$ = 5.7, $J_{3'-4'}$ = 3.3, H-3'), 6.52 (bd, 1H, $J_{2'-3'}$ = 5.7, H-2'), 7.21 (bs, 2H, NH_2), 8.13 (s, 1H, H-2), 8.26 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): 26.78 (C-5'), 29.75 (C-6'), 40.28 (C-4'), 52.05 (C-7'), 70.38 (C-1'), 119.86 (C-5), 135.08 (C-2'), 136.14 (C-3'), 139.67 (C-8), 150.29 (C-4), 152.41 (C-2), 156.31 (C-6). ESI MS *m/z* (%): 228.3 (100) [M+H], 250.3 (5) [M+Na]; HRMS ESI ($C_{12}H_{14}N_5$) calculated: 228.12437, found: 228.12424. For $C_{12}H_{13}N_5$ (227.27) calculated: 63.42% C, 5.77% H, 30.82% N; found: 63.68% C, 6.07% H, 30.85% N.



1-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]heptane-2,3-diol (376)

To a solution of **374** (145 mg, 0,59 mmol) in dioxane - water mixture (4:1, 20 mL) was added NMMO (50 *w* solution in water) and OsO_4 (60 μL) and the reaction mixture was stirred at room temperature for 48 h. Volatiles were evaporated, crude compound was adsorbed on silica gel and purified by chromatography on silica gel (ethyl acetate - toluene - acetone - ethanol 17:4:3:1). Subsequent Crystallization from toluene - ethyl acetate mixture afforded **376** (130 mg, 78%) as white crystals (m.p. = 209°C).

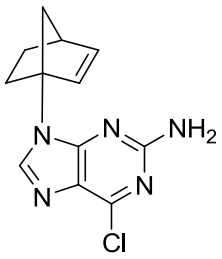
^{1}H NMR (500 MHz, DMSO): 1.38 (m, 1H, H-5endo), 1.71 – 1.82 (m, 2H, H-5exo, H-6exo), 1.89 (dm, 1H, J_{gem} = 9.5, H-7b), 2.13 (m, 1H, H-4), 2.33 (m, 1H, H-6endo), 2.50 (m, 1H, H-7a), 3.84 (m, 1H, H-3), 4.10 (td, 1H, J_{2-3} = J_{2-OH} = 6.1, J_{2-7b} = 1.7, H-2), 4.76 (d, 1H, J_{OH-2} = 6.1, 2-OH), 5.04 (d, 1H, J_{OH-3} = 4.9, 3-OH), 8.61 (s, 1H, H-8'), 8.75 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): 24.15 (C-5), 29.67 (C-6), 34.71 (C-7), 41.03 (C-4), 68.47 (C-1), 72.51 (C-2), 73.51 (C-3), 131.46 (C-5'), 147.69 (C-8'), 149.07 (C-6'), 151.22 (C-2'), 152.71 (C-4'). ESI MS *m/z* (%): 279.1 (100) [M-H]. For $C_{12}H_{13}N_4O_2Cl$ (280.71) calculated: 51.34% C, 4.67% H, 19.96% N, 12.63% Cl; found: 51.40% C, 4.63% H, 19.92% N, 12.57% Cl.



(1*R,2*R**,3*S**,4*R**)-1-(6-amino-9*H*-purin-9-yl)bicyclo[2.2.1] heptane-2,3-diol (377)**

Ammonolysis was performed according to method **F2** starting from **376** (100 mg, 0.36 mmol). Poorly soluble product was filtered off and washed thoroughly with water and methanol. Yield 60 mg, 64%, white powder (m.p. = 324°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): δ 1.34 (m, 1H, H-5endo), 1.64 - 1.75 (m, 2H, H-5exo, H-6exo), 1.83 (dm, 1H, J_{gem} = 9.5, H-7b), 2.09 (m, 1H, H-4), 2.29 (m, 1H, H-6endo), 2.39 (dm, 1H, J_{gem} = 9.5, H-7a), 3.80 (m, 1H, H-3), 4.09 (td, 1H, $J_{2,3}$ = $J_{2,OH}$ = 6.1, $J_{2,7b}$ = 1.7, H-2), 4.67 (d, 1H, $J_{OH,2}$ = 6.1, 2-OH), 5.05 (d, 1H, $J_{OH,3}$ = 5.0, 3-OH), 7.09 (bs, 2H, NH_2), 8.00 (s, 1H, H-8'), 8.09 (s, 1H, H-2'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.31 (C-5), 30.03 (C-6), 34.64 (C-7), 41.05 (C-4), 67.53 (C-1), 72.32 (C-2), 73.50 (C-3), 119.48 (C-5'), 140.83 (C-8'), 150.40 (C-4'), 152.05 (C-2'), 156.11 (C-6'). ESI MS *m/z* (%): 262.1 (100) [M+H], 284.1 (73) [M+Na]; HRMS ESI ($C_{12}H_{16}O_2N_5$) calculated: 262.12985; found: 262.12983. For $C_{12}H_{15}N_5O_2$ (261.28) calculated: 55.16% C, 5.79% H, 26.80% N; found: 55.30% C, 5.88% H, 26.65% N.

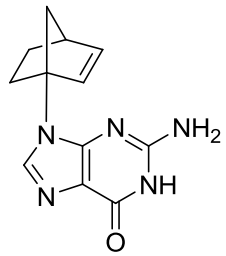


9-[(1*R,4*R**)-Bicyclo[2.2.1]hept-2-en-1-yl]-6-chloro-9*H*-purin-2-amine (378)**

2-Amino-6-chloropurine nucleobase was constructed according to method **A** (316 mg, 2.2 mmol of **373**, *n*-BuOH as a solvent, 160°C for 2h in MW reactor). Mobile phase 30-50% ethyl acetate in hexane. Crystallization from hexane - ethyl acetate mixture. Yield 330 mg, 57% as white ctystals (m.p. = 159°C).

^{1}H NMR (500 MHz, DMSO): δ 1.22 (m, 1H, H-5'endo), 1.82 (m, 1H, H-6'exo), 1.95 (dm, 1H, J_{gem} = 7.7, H-7'b), 1.99 (m, 1H, H-5'exo), 2.08 (dm, 1H, J_{gem} = 7.8, H-7'a), 2.16 (m, 1H, H-6'endo), 2.99 (m, 1H, H-4'), 6.27 (dd, 1H, $J_{3',2'}$= 5.7, $J_{3',4'}$ = 3.2, H-3'), 6.48 (bd, 1H, $J_{2',3'}$= 5.7, H-2'), 6.86 (bs, 2H, NH_2), 8.24 (s, 1H, H-8),. ^{13}C NMR (125.8 MHz, DMSO): δ 26.67 (C-5'), 29.47 (C-6'), 40.19 (C-4'), 51.83 (C-7'), 70.39 (C-1'), 124.32 (C-5), 134.82 (C-2'), 136.27 (C-3'), 142.12 (C-8), 149.72 (C-6), 154.75 (C-4), 159.64 (C-2). ESI MS *m/z* (%): 262.1 (26) [M+H]; 284.1 (100) [M+Na]; HRMS ESI ($C_{12}H_{13}N_5Cl$) calculated: 262.08540, found: 262.08543. For

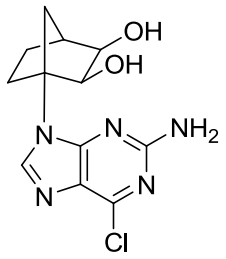
$C_{12}H_{12}ClN_5$ (261.71) calculated: 55.07% C, 4.62% H, 13.55% Cl, 26.76 % N; found: 55.25% C, 4.75% H, 13.42% Cl, 26.98 % N.



2-Amino-9-[(1*R,4*R**)-bicyclo[2.2.1]hept-2-en-1-yl]-1,9-dihydro-6*H*-purin-6-one (379)**

Hydrolysis to guanine derivative was performed according to method **J** starting from **378** (100 mg, 0.46 mmol). Crystallization from methanol Yield 75 mg, 81%, white powder (m.p. > 330°C (decomp.)).

^{1}H NMR (600 MHz, DMSO): δ1.20 (m, 1H, H-5'endo), 1.78 (m, 1H, H-6'exo), 1.91 (dm, 1H, J_{gem} = 7.7, H-7'b), 1.94 - 2.01 (m, 2H, H-5'exo, H-7'a), 2.07 (ddd, 1H, J_{gem} = 10.9, $J_{6'en,5'en}$= 9.5, $J_{6'en,5'ex}$ = 4.0, H-6'endo), 2.95 (m, 1H, H-4'), 6.24 (dd, 1H, $J_{3',2'}$= 5.7, $J_{3',4'}$ = 3.2, H-3'), 6.43 - 6.46 (m, 3H, H-2', NH_2), 7.80 (s, 1H, H-8), 10.65 (bs, 1H, H-1). ^{13}C NMR (150 MHz, DMSO): δ26.88 (C-5'), 29.83 (C-6'), 40.17 (C-4'), 51.98 (C-7'), 70.14 (C-1'), 117.77 (C-5), 135.28 (C-2'), 136.00 (C-3'), 136.23 (C-8), 151.94 (C-4), 153.25 (C-2), 157.00 (C-6). ESI MS *m/z* (%): 216.1 (65) [M+H], 244.2 (100) [M+Na]; HRMS ESI ($C_{12}H_{14}ON_5$) calculated: 244.11929, found: 244.11929. For $C_{12}H_{13}N_5O$ (243.26) calculated: 59.25% C, 5.39% H, 28.79% N; found: 59.17% C, 5.33% H, 28.92% N.

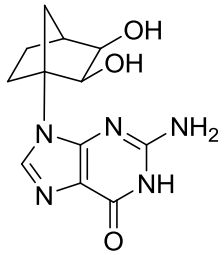


(1*R,2*R**,3*S**,4*R**)-1-(2-Amino-6-chloro-9*H*-purin-9-yl) bicyclo[2.2.1]heptane-2,3-diol (380)**

To a solution of **378** (280 mg, 1.1 mmol) in dioxane - water mixture (3:1, 32 mL) was added NMMO (50% *w* solution in water) and OsO_4 (100 μL) and the reaction mixture was stirred at room temperature for 48 h. Volatiles were evaporated, crude compound was adsorbed on silica gel and chromatographed (ethyl acetate - acetone - ethanol - water 100:15:6:4) and subsequent Crystallization from ethyl acetate - ethanol mixture afforded **380** (268 mg, 85%) as white crystals (m.p. = 224°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): δ1.32 (m, 1H, H-5endo), 1.64 - 1.74 (m, 2H, H-5exo, H-6exo), 1.80 (dm, 1H, J_{gem} = 9.6, H-7b), 2.08 (m, 1H, H-4), 2.25 (m, 1H, H-6endo), 2.37 (dm, 1H, J_{gem} = 9.5, H-7a), 3.78 (m, 1H, H-3), 4.05 (td, 1H, $J_{2,3}$ = $J_{2,OH}$ = 6.0, $J_{2,7b}$ = 1.6, H-2), 4.75 (d, 1H, $J_{OH,2}$ = 6.1, 2-**OH**), 5.02 (d, 1H, $J_{OH,3}$ = 5.0, 3-

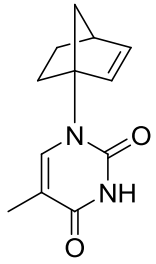
OH), 6.75 (bs, 2H, NH_2), 8.01 (s, 1H, H-8'). ^{13}C NMR (125.8 MHz, DMSO): δ 24.14 (C-5), 29.58 (C-6), 34.55 (C-7), 41.01 (C-4), 67.63 (C-1), 72.01 (C-2), 73.47 (C-3), 124.07 (C-5'), 143.40 (C-8'), 149.29 (C-6'), 154.88 (C-4'), 159.43 (C-2'). ESI MS *m/z* (%): 296.1 (33) [M+H], 318.1 (100) [M+Na]; HRMS ESI ($C_{12}H_{15}O_2N_5Cl$) calculated: 296.09088, found: 296.09082. For $C_{12}H_{14}ClN_5O_2$ (295.72) calculated: 48.72% C, 4.77% H, 11.99% Cl, 23.68 % N; found: 48.74% C, 4.82% H, 11.83% Cl, 23.39 % N.



2-Amino-9-[(1*R,2*R**,3*S**,4*R**)-2,3-dihydroxybicyclo[2.2.1] hept-1-yl]-1,9-dihydro-6*H*-purin-6-one (381)**

Hydrolysis to guanine derivative was performed according to method **J** starting from **380** (100 mg, 0.46 mmol). Crystallization from methanol Yield 97 mg, 85%, white powder (m.p. > 360°C (decomp.)).

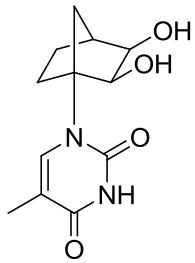
^{1}H NMR (600 MHz, DMSO): δ1.28 (m, 1H, H-5endo), 1.59 (td, 1H, J_{gem} = $J_{6ex,5ex}$= 12.4, $J_{6ex,5en}$ = 4.1, H-6exo), 1.67 (tt, 1H, J_{gem} = $J_{5ex,6ex}$= 12.5, $J_{5ex,6en}$ = $J_{5ex,4}$ = 4.8, H-5exo), 1.74 (dm, 1H, J_{gem} = 9.5, H-7b), 2.04 (dm, 1H, $J_{4,5ex}$ = 4.9, H-4), 2.20 (m, 1H, H-6endo), 2.28 (dm, 1H, J_{gem} = 9.5, H-7a), 3.74 (m, 1H, H-3), 4.04 (td, 1H, $J_{2,3}$ = $J_{2,OH}$ = 6.1, $J_{2,7b}$ = 1.7, H-2), 4.70 (d, 1H, $J_{OH,2}$ = 6.1, 2-**OH**), 5.02 (d, 1H, $J_{OH,3}$ = 5.0, 3-**OH**), 6.32 (bs, 2H, NH_2), 7.54 (s, 1H, H-8'), 10.45 (bs, 1H, H-1'). ^{13}C NMR (150 MHz, DMSO): δ 24.35 (C-5), 29.98 (C-6), 34.63 (C-7), 41.04 (C-4), 67.32 (C-1), 72.09 (C-2), 73.54 (C-3), 117.45 (C-5'), 137.51 (C-8'), 151.99 (C-4'), 152.86 (C-2'), 157.11 (C-6'). ESI MS *m/z* (%): 278.2 (12) [M+H], 300.2 (100) [M+Na]; HRMS ESI ($C_{12}H_{16}O_3N_5$) calculated: 278.12477, found: 278.12482. For $C_{12}H_{15}N_5O_3$ (277.28) calculated: 51.98% C, 5.45% H, 25.26% N; found: 52.26% C, 5.52% H, 25.12% N.



1-[(1*R,4*R**)-Bicyclo[2.2.1]hept-2-en-1-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (382)**

Thymine nucleobase construction was performed according to method **E** starting from **373** (206 mg, 1.43 mmol). Mobile phase: 60-80% ethyl acetate in hexane. Crystallization from toluene - ethyl acetate mixture. Yield 180 mg, 58%, colorless needles (m.p. = 231°C).

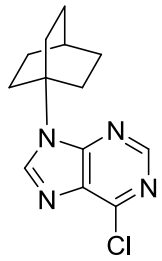
^{1}H NMR (500 MHz, DMSO): δ1.18 (m, 1H, H-5'endo), 1.67 (m, 1H, H-6'exo), 1.76 (dm, 1H, J_{gem} = 7.6, H-7'b), 1.77 (d, 3H, $J_{CH3,6'}$ = 1.2, CH_3), 1.81 (dm, 1H, J_{gem} = 7.6, H-7a), 1.89 - 1.95 (m, 2H, H-5'exo, H-6'endo), 2.89 (m, 1H, H-4'), 6.15 (dd, 1H, $J_{3',2'}$= 5.7, $J_{3',4'}$ = 3.3, H-3'), 6.34 (bd, 1H, $J_{2',3'}$ = 5.7, H-2'), 7.45 (q, 1H, $J_{6,CH3}$ = 1.2, H-6), 11.23 (bs, 1H, H-3). ^{13}C NMR (125.8 MHz, DMSO): δ12.17 (CH_3), 27.37 (C-5'), 29.22 (C-6'), 39.16 (C-4'), 51.81 (C-7'), 74.63 (C-1'), 74.63 (C-1'), 108.23 (C-5), 135.42 (C-3'), 135.79 (C-2'), 139.34 (C-6), 151.22 (C-2), 164.36 (C-4). ESI MS *m/z* (%): 219.2 (100) [M+H], 241.1 (83) [M+Na]; HRMS ESI ($C_{12}H_{15}O_2N_5$) calculated: 219.11280, found: 219.11277. For $C_{12}H_{14}N_2O_2$ (218.25) calculated: 66.04% C, 6.47% H, 12.84% N; found: 65.87% C, 6.37% H, 12.95% N.



1-[(1*R,2*R**,3*S**,4*R**)-2,3-Dihydroxybicyclo[2.2.1]hept-1-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (383)**

To a solution of **382** (100 mg, 0.46 mmol) in dioxane - water mixture (4:1, 10 mL) was added NMMO (50% *w* solution in water) and OsO_4 (40 μL), and the reaction mixture was stirred at room temperature for 48 h. Volatiles were evaporated, crude compound was adsorbed on silica gel, chromatographed (ethyl acetate - acetone - ethanol - water 100:15:6:4) and subsequent Crystallization from ethyl acetate afforded **383** (90 mg, 78%) as white crystals (m.p. = 264°C).

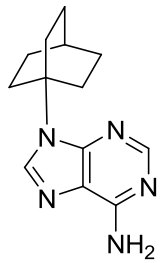
^{1}H NMR (500 MHz, DMSO): δ1.25 (m, 1H, H-5endo), 1.46 (td, 1H, J_{gem} = $J_{6ex,5ex}$= 12.6, $J_{6ex,5en}$ = 4.4, H-6exo), 1.56 (dm, 1H, J_{gem} = 9.3, H-7b), 1.62 (tt, 1H, J_{gem} = $J_{5ex,6ex}$= 12.6, $J_{5ex,6en}$ = $J_{5ex,4}$ = 4.9, H-5exo), 1.75 (d, 3H, $J_{CH3,6'}$ = 1.1, CH_3), 1.96 (dm, 1H, $J_{4,5ex}$ = 5.0, H-4), 2.10 (dm, 1H, J_{gem} = 9.4, H-7a), 2.16 (m, 1H, H-6endo), 3.69 (m, 1H, H-3), 4.12 (td, 1H, $J_{2,3}$ = $J_{2,OH}$ = 6.0, $J_{2,7b}$ = 1.5, H-2), 4.82 (d, 1H, $J_{OH,3}$ = 4.9, 3-**OH**), 4.87 (d, 1H, $J_{OH,2}$ = 5.8, 2-**OH**), 7.35 (q, 1H, $J_{6',CH3}$ = 1.2, H-6'), 11.06 (bs, 1H, H-3'). ^{13}C NMR (125.8 MHz, DMSO): δ12.17 (CH_3), 24.33 (C-5), 28.86 (C-6), 35.28 (C-7), 40.02 (C-4), 70.81 (C-2), 72.13 (C-1), 73.35 (C-3), 106.85 (C-5'), 141.42 (C-6'), 151.03 (C-2'), 164.49 (C-4'). ESI MS *m/z* (%): 253.2 (21) [M+H], 275.2 (100) [M+Na]; HRMS ESI ($C_{12}H_{17}O_4N_2$) calculated: 253.11828, found: 253.11827. For $C_{12}H_{16}N_2O_4$ (252.27) calculated: 57.13% C, 6.39% H, 11.10% N; found: 57.00% C, 6.29% H, 11.32% N.



9-(Bicyclo[2.2.2]oct-1-yl)-6-chloro-9H-purine (386)

6-Chloropurine nucleobase was constructed according to method **C1** (160 mg, 0.95 mmol of **385**[134], EtOH as a solvent, 105°C for 6d in sealed vessel). Mobile phase toluene - ethyl acetate 10:1. Crystallization from water - methanol mixture. Yield 162 mg, 65% as white crystals (m.p. = 170°C).

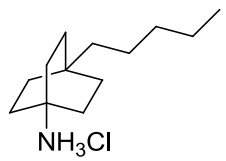
^{1}H NMR (500 MHz, $CDCl_3$): 1.81 (sept, 1H, $J_{4'-3'}$ = 3.1, H-4'), 1.89 (m, 6H, H-3'), 2.34 (m, 6H, H-2'), 8.17 (s, 1H, H-8), 8.72 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 23.50 (C-4'), 26.02 (C-3'), 30.29 (C-2'), 58.54 (C-1'), 132.82 (C-5), 142.88 (C-8), 150.51 (C-2), 150.99 (C-6), 152.03 (C-4). ESI MS *m/z* (%): 263 (100) [M+H], 285 (43) [M+Na]. For $C_{14}H_{17}N_4Cl$ (262.73) calculated: 59.43% C, 5.75% H, 21.32% N, 13.49% Cl; found: 59.22% C, 5.74% H, 21.04% N, 13.57% Cl.



9-(Bicyclo[2.2.2]oct-1-yl)-9H-purin-6-amine (387)

Ammonolysis was performed according to method **F1** starting from **386** (100 mg, 0.38 mmol). Mobile phase: 2-6% methanol in ethyl acetate. Crystallization from water - methanol mixture. Yield 77 mg, 83% as white plates (m.p. = 270°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): 1.67 (sept, 1H, $J_{4'-3'}$ = 3.0, H-4'), 1.75 (m, 6H, H-3'), 2.23 (m, 6H, H-2'), 7.12 (bs, 2H, NH_2), 8.05 (s, 1H, H-8), 8.10 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): 23.45 (C-4'), 25.91 (C-3'), 29.81 (C-2'), 56.44 (C-1'), 120.40 (C-5), 138.40 (C-8), 149.92 (C-4), 151.45 (C-2), 156.39 (C-6). ESI MS *m/z* (%): 244.3 (100) [M+H], 266.3 (5) [M+Na]; HRMS ESI ($C_{13}H_{18}N_5$) calculated: 244.15567, found: 244.15556. For $C_{13}H_{17}N_5$ (243.31) calculated: 64.17% C, 7.04% H, 27.78% N; found: 64.17% C, 7.24% H, 28.54% N.

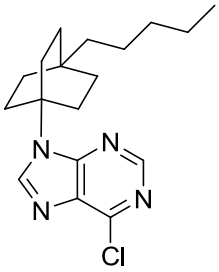


4-Pentylbicyclo[2.2.2]octan-1-amine hydrochloride (389)

Curtius rearrangement was performed according to **Method D** starting from commercially available **388** (1.2 g, 5.4 mmol). Precipitation with Et_2O from ethanolic solution. Yield 1.1 g, 89%, white plates (m.p. = 282°C).

^{1}H NMR (500 MHz, DMSO): 0.84 (t, 3H, $J_{5'-4'}$ = 7.2, H-5'), 1.04 (m, 2H, H-1'), 1.10 - 1.20 (m, 4H, H-2', H-3'), 1.25 (m, 2H, C-4'), 1,41 (m, 6H, H-3), 1.68 (m, 6H, H-2), 8.12 (bs, 3H, NH_3). ^{13}C NMR (125.8 MHz, DMSO): 14.09 (C-5'), 22.26 (C-

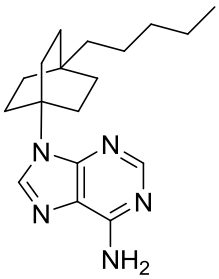
4'), 22.97 (C-2'), 29.47 (C-2), 29.99 (C-4), 30.21 (C-3), 32.35 (C-3'), 40.49 (C-1'), 50.84 (C-1). ESI MS *m/z* (%): 196.2 (100) [M+H]. For $C_{13}H_{24}NCl$ (229.79) calculated: 67.95% C, 10.53% H, 6.10% N, 15.43% Cl; found: 67.61% C, 10.45% H, 5.93% N, 15.34% Cl.



6-Chloro-9-(4-pentylbicyclo[2.2.2]oct-1-yl)-9H-purine (390)

6-Chloropurine nucleobase was constructed according to method **C2** (600 mg, 2.6 mmol of **389**, *n*-BuOH as a solvent, 160°C for 4h in MW reactor. Mobile phase: 10-25% ethyl acetate in hexane. Crystallization from cyclohexane - pentane mixture. Yield 420 mg, 49% as white ctystals (m.p. = 122°C).

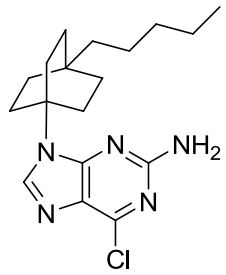
^{1}H NMR (500 MHz, $CDCl_3$): 0.90 (t, 3H, $J_{5'',4''}$ = 7.2, H-5''), 1.16 - 1.26 (m, 6H, H-1'', H-2'', H-3''), 1.31 (m, 2H, C-4''), 1.68 (m, 6H, H-3'), 2.35 (m, 6H, H-2'), 8.15 (s, 1H, H-8), 8.71 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.05 (C-5''), 22.64 (C-4''), 23.39 (C-2''), 30.23 (C-4'), 30.75 (C-2'), 30.96 (C-3'), 32.66 (C-3''), 40.18 (C-1''), 58.81 (C-1'), 132.85 (C-5), 142.96 (C-8), 150.57 (C-2), 151.07 (C-6), 152.12 (C-4). ESI MS *m/z* (%): 333.2 (100) [M+H], 355.2 (11) [M+Na]. For $C_{18}H_{25}N_4Cl$ (332.87) calculated: 64.95% C, 7.57% H, 16.83% N, 10.65% Cl; found: 64.83% C, 7.62% H, 16.65% N, 10.84% Cl.



9-(4-Pentylbicyclo[2.2.2]oct-1-yl)-9H-purin-6-amine (391)

Ammonolysis was performed according to method **F1** starting from **390** (110 mg, 0.3 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water - methanol mixture. Yield 89 mg, 86%, white crystals (m.p. = 209°C).

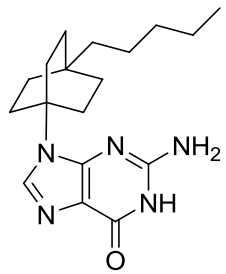
^{1}H NMR (500 MHz, DMSO): 0.84 (t, 3H, $J_{5'',4''}$ = 7.2, H-5''), 1.12 and 1.18 - 1.23 (m, 6H, H-1'', H-2'', H-3''), 1.28 (m, 2H, C-4''), 1.56 (m, 6H, H-3'), 2.25 (m, 6H, H-2'), 7.13 (bs, 2H, NH_2), 8.06 (s, 1H, H-8), 8.09 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): 14.13 (C-5''), 22.29 (C-4''), 23.04 (C-2''), 29.99 (C-4'), 30.18 (C-2'), 30.81 (C-3'), 32.41 (C-3''), 40.78 (C-1''), 56.73 (C-1'), 120.35 (C-5), 138.53 (C-8), 149.92 (C-4), 151.44 (C-2), 156.35 (C-6). ESI MS *m/z* (%): 314.2 (100) [M+H]. For $C_{18}H_{27}N_5$ (313.44) calculated: 68.97% C, 8.68% H, 22.34% N; found: 68.61% C, 8.70% H, 22.11% N.



6-Chloro-9-(4-pentylbicyclo[2.2.2]oct-1-yl)-9H-purin-2-amine (392)

2-Amino-6-chloropurine nucleobase was constructed according to method **A** (142 mg, 0.88 mmol of **389**, *n*-BuOH as a solvent, 160°C for 2h in MW reactor). Mobile phase 30-50% ethyl acetate in hexane. Crystallization from cyclohexane. Yield 175 mg, 57% as white ctystals (m.p. = 182°C).

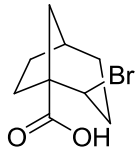
^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89 (t, 3H, $J_{5'',4''}$ = 7.3, H-5''), 1.16 (m, 2H, H-1''), 1.19 - 1.25 (m, 4H, H-2'', H-3''), 1.31 (m, 2H, H-4''), 1.63 (m, 6H, H-3'), 2.26 (m, 6H, H-2'), 5.14 (bs, 2H, NH_2), 7.85 (s, 1H, H-8). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.06 (C-5''), 22.65 (C-4''), 23.40 (C-2''), 30.14 (C-4'), 30.35 (C-2'), 30.94 (C-3'), 32.67 (C-3''), 40.89 (C-1''), 57.90 (C-1'), 126.38 (C-5), 140.31 (C-8), 151.10 (C-6), 154.00 (C-4), 157.84 (C-2). ESI MS *m/z* (%): 348.2 (50) [M+H], 370.2 (100) [M+Na]; HRMS ESI ($C_{18}H_{27}N_5Cl$) calculated: 348.19495, found: 348.19489. For $C_{18}H_{26}ClN_5$ (348.89) calculated: 62.14% C, 7.53% H, 10.19% Cl, 20.13 % N; found: 62.19% C, 7.47% H, 10.00% Cl, 19.91 % N.



2-Amino-9-(4-butylbicyclo[2.2.2]oct-1-yl)-1,9-dihydro-6H-purin-6-one (393)

Hydrolysis to guanine derivative was performed according to method **J** starting from **392** (90 mg, 0.46 mmol). Crystallization from methanol Yield 61 mg, 72%, white powder (m.p. > 360°C (decomp.)).

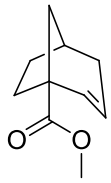
^{1}H NMR (500 MHz, DMSO): δ 0.86 (t, 3H, $J_{5'',4''}$ = 7.2, H-5''), 1.15 - 1.24 (m, 6H, H-1'', H-2'', H-3''), 1.28 (m, 2H, H-4''), 1.51 (m, 6H, H-3'), 2.18 (m, 6H, H-2'), 6.39 (bs, 2H, NH_2), 7.62 (s, 1H, H-8), 10.58 (bs, 1H, H-1). ^{13}C NMR (125.8 MHz, DMSO): δ 14.13 (C-5''), 22.30 (C-4''), 23.01 (C-2''), 29.91 (C-4'), 30.01 (C-2'), 30.86 (C-3'), 32.40 (C-3''), 40.79 (C-1''), 56.38 (C-1'), 118.44 (C-5), 135.11 (C-8), 151.51 (C-4), 152.24 (C-2), 157.05 (C-6). ESI MS *m/z* (%): 344.2 (27) [M+H], 352.3 (100) [M+Na]; HRMS ESI ($C_{18}H_{28}ON_5$) calculated: 330.22884, found: 330.22877. For $C_{18}H_{27}N_5O$ (329.44) calculated: 65.62% C, 8.26% H, 21.26% N; found: 65.90% C, 8.31% H, 21.19% N.



(1*S,2*S**,5*S**)-2-Bromobicyclo[3.2.1]octane-1-carboxylic acid (395)**[135a]

A mixture of **394** (4,5 g, 29 mmol), bromine (1.8 mL, 35 mmol) and PCl_3 (0,3 mL) was heated to 80°C for 8 hours under reflux condenser. Reaction mixture (solidifies on cooling) was dissolved in diethylether (100 mL) and washed with water (2 x 100 mL), saturated sodium thiosulfate (2 x 100 mL) and water (100 mL). Organic phase was dried over sodium sulfate and evaporated. The residue was crystallized from cyclohexane to provide **395** (3.7 g, 55%) as a white powder (m.p. = 148°C).

^{1}H NMR (500 MHz, DMSO): δ 1.34 (m, 1H, H-4eq), 1.47 (m, 1H, H-6endo), 1.62 (m, 1H, H-4ax), 1.76 - 1.86 (m, 5H, H-3eq, H-6ex, H-7, H-8b), 1.97 (dm, 1H, J_{gem} = 12.0, H-8a), 2.20 (dddd, 1H, J_{gem} = 16.0, $J_{3ax-4ax}$ = 13.1, $J_{3ax-4eq}$ = 5.7, J_{3ax-2} = 4.5, H-3ax), 2.26 (m, 1H, H-5), 4.74 (m, 1H, H-2), 12.39 (bs, 1H, OH). ^{13}C NMR (125.8 MHz, DMSO): δ 27.06 (C-4), 27.59 (C-6), 28.95 (C-3), 34.12 (C-7), 34.59 (C-5), 36.02 (C-8), 55.53 (C-1), 59.44 (C-2), 175.38 (COO). ESI MS *m/z* (%): 255.1 (100) [M+Na]. For $C_9H_{13}BrO$ (233.10) calculated: 46.37% C, 5.62% H, 34.28% Br; found: 46.27% C, 5.58% H, 34.54% Br.

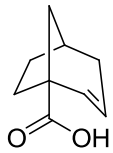


Methyl (1*S,5*R**)-bicyclo[3.2.1]oct-2-ene-1-carboxylate (397)**

To a solution of **395** (1.3 g, 5.7 mmol) in diethylether (50 mL) 1M solution of diazomethane was added dropwise, until nitrogen ceased evolving and solution acquired a slightly yellow color. Diethylether was removed *in vacuo* to provide GC-MS pure **396** (99%), which was then dissolved in DMF (15 mL) and DBU (1.8 g, 11.5 mmol) was added. Reaction mixture was heated at 80°C overnight, diluted with water (100 mL) and extracted with hexane (5 x 50 mL). Oganic extracts were dried over sodium sulfate and evaporated. Resulting brownish oil was purified by column chromatography (hexane - ethyl acetate 20:1) to afford **397** (860 mg, 91%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.52 (m, 1H, H-6endo), 1.80 (dm, 1H, J_{gem} = 10.7, H-8b), 1.88 (dm, 1H, J_{gem} = 18.0, H-4b), 1.96 (ddt, 1H, J_{gem} = 10.7, J_{8a-5} = 5.6, J_{8a-6en} = J_{8a-7en} = 1.4, H-8a), 2.01 - 2.09 (m, 3H, H-6exo, H-7), 2.36 (dm, 1H, J_{gem} = 17.9, H-4a), 2.47 (m, 1H, H-5), 5.51 (dddd, 1H, J_{3-2} = 9.7, J_{3-4b} = 4.2, J_{3-4a} = 2.5, J_{3-5} = 1.3, H-3), 6.12 (dm, 1H, J_{2-3} = 9.7, H-2. ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.58 (C-6), 33.83 (C-5), 36.53 (C-4), 39.16 (C-8), 40.51 (C-7), 50.20 (C-1), 51.85 (CH_3), 124.67 (C-3),

132.40 (C-2), 176.51 (COO). ESI MS *m/z* (%): 167.2 (100) [M+H]; HRMS ESI ($C_{10}H_{15}O_2$) calculated: 167.10720, found: 167.10800. For $C_{10}H_{15}O_2$ (167.22) calculated: 71.82% C, 9.04% H; found: 71.65% C, 9.15% H.



(1*S,5*R**)-Bicyclo[3.2.1]oct-2-ene-1-carboxylic acid (398)**

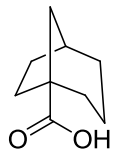
To a solution of **397** (800 mg, 4.8 mmol) in methanol (20 mL) a solution of NaOH (0.6 g, 15 mmol) in water (10 mL) was added, and this mixture was stirred at RT overnight. Methanol was evaporated, reaction mixture was diluted with water to approx 100 mL and washed with diethylether (2 x 50 mL). Water layer was acidified with conc. HCl and product was extracted into diethylether (3 x 100 mL). Combined organic extracts were dried over sodium sulfate and evaporated to afford **398** (680 mg, 93 %) as colorless oil.

^{1}H NMR (500 MHz, DMSO): δ 1.43 (m, 1H, H-6endo), 1.65 (dm, 1H, J_{gem} = 10.6, H-8b), 1.80 - 1.88 (m, 2H, H-4exo, H-8a), 1.91 - 2.01 (m, 3H, H-6exo, H-7), 2.29 (dm, 1H, J_{gem} = 17.7, H-4endo), 2.41 (m, 1H, H-5), 5.46 (dm 1H, J_{3-2} = 9.7, H-3), 6.06 (dm, 1H, J_{2-3} = 9.7, H-2), 12.27 (bs, 1H, OH). ^{13}C NMR (125.8 MHz, DMSO): δ 30.44 (C-6), 33.51 (C-5), 36.30 (C-4), 38.89 (C-8), 40.34 (C-7), 49.60 (C-1), 124.37 (C-3), 133.13 (C-2), 176.87 (COO). ESI MS *m/z* (%): 153.2 (100) [M+H]; HRMS ESI ($C_9H_{13}O_2$) calculated: 153.09155, found: 153.09198. For $C_9H_{12}O_2$ (152.19) calculated: 71.03% C, 7.95% H; found: 70.66% C, 7.87% H.

(1*S,5*R**)-Bicyclo[3.2.1]oct-2-en-1-amine hydrochloride (399)**

Curtius rearrangement was performed according to **Method D** starting from **398** (600 mg, 3.9 mmol). Precipitation with ethyl acetate from methanolic solution. Yield 450 mg, 73%, white crystals (m.p. = 280°C (decomp.)).

^{1}H NMR (500 MHz, DMSO): δ 1.41 (m, 1H, H-6endo), 1.70 (dm, 1H, J_{gem} = 10.1, H-8b), 1.84 - 1.91 (m, 3H, H-4exo, H-7b, H-8a), 1.97 - 2.04 (m, 2H, H-6exo, H-7a), 2.30 (dm, 1H, J_{gem} = 18.2, H-4endo), 2.42 (m, 1H, H-5), 5.58 (dm, 1H, J_{3-2} = 9.7, H-3), 5.82 (dm, 1H, J_{2-3} = 9.7, H-2), 8.58 (bs, 3H, NH_3). ^{13}C NMR (125.8 MHz, DMSO): δ 29.18 (C-6), 32.33 (C-5), 35.99 (C-4), 38.52 (C-8), 38.84 (C-7), 58.27 (C-1), 126.36 (C-3), 132.05 (C-2). HRMS ESI ($C_8H_{14}N$) calculated: 124.11262, found: 124.11287. For $C_8H_{12}NCl$ (157.64) calculated: 60.95% C, 7.67% H, 8.89% N, 22.49% Cl; found: 60.98% C, 7.85% H, 8.71% N, 22.61% Cl.



(1*R,5*S**)-Bicyclo[3.2.1]octane-1-carboxylic acid (401)**

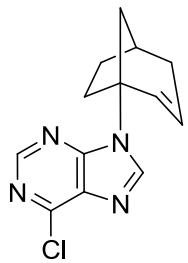
A mixture of **396** (1 g, 6.01 mmol) and 20% $Pd(OH)_2/C$ (100 mg) in abs. MeOH (20 mL) was treated with hydrogen (5 atm) until the consumption of hydrogen ceased. Catalyst was filtered off on a celite pad and methanol was evaporated to afford **400** (0.757 g, 76%, >98% pure on GC-MS analysis) as clear oil, which was used directly in the next reaction.

To a solution of **400** (757 mg, 4.5 mmol) in methanol (20 mL) a solution of NaOH (0.6 g, 15 mmol) in water (10 mL) was added, and this mixture was stirred at RT overnight. Methanol was evaporated, reaction mixture was diluted with water to approx 100 mL and washed with diethylether (2 x 50 mL). Water layer was acidified with conc. HCl and product was extracted with diethylether (3 x 100 mL). Combined organic extracts were dried over sodium sulfate and evaporated to afford **401** (379 mg, 53 %) as colorless oil. Spectral characteristics match those described in literature.[151]

(1*S,5*S**)-*N*-Bicyclo[3.2.1]octan-1-amine hydrochloride (402)**

Curtius rearrangement was performed according to Method **D** starting from **401** (370 mg, 2.9 mmol). Precipitation with ethyl acetate from methanolic solution. Yield 317 mg, 83%, white crystals (m.p. = 244°C).

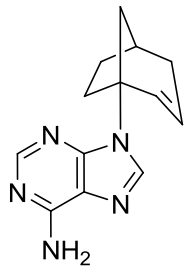
^{1}H NRM (500 MHz, DMSO): δ 1.30 (m, 1H, H-4b), 1.37-1.45 (m, 3H, H-4a, H-6endo, H-8b), 1.50-1.66 (m, 4H, H-2, H-3), 1.69-1.73 (m, 2H, H-7), 1.77-1.83 (m, 2H, H-8a, H-6exo), 2.24 (m, 1H, H-5), 8.31 (bs, 3H, NH_3). ^{13}C NMR (125.8 MHz, DMSO): δ 18.76 (C-3), 27.53 (C-6), 30.60 (C-4), 32.22 (C-7), 34.47 (C-5), 35.55 (C-2), 42.08 (C-8), 59.39 (C-1). HRMS ESI ($C_8H_{16}N$) calculated: 126.12773, found: 126.12761. For $C_8H_{16}NCl$ (161.67) calculated: 59.43% C, 9.98% H, 8.66% N, 21.93% Cl; found: 59.55% C, 9.91% H, 8.77% N, 21.80% Cl.



9-[(1*S,5*R**)-Bicyclo[3.2.1]oct-2-en-1-yl]-6-chloro-9H-purine (403)**

6-Chloropurine nucleobase was constructed according to method **C1** (600 mg, 2.6 mmol of **389**, *n*-BuOH as a solvent, 160°C for 4h in MW reactor. Mobile phase: 20-40% ethyl acetate in hexane. Crystallization from cyclohexane - pentane mixture. Yield 550 mg, 55% as white ctystals (m.p. = 101°C).

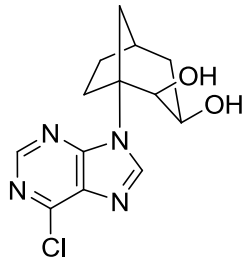
^{1}H NMR (500 MHz, $CDCl_3$):1.71 (m, 1H, H-6'endo), 2.06 (dm, 1H, J_{gem} = 18.1, H-4'b), 2.18 - 2.28 (m, 3H, H-6'exo, H-7'exo, H-8'b), 2.54 (dm, 1H, J_{gem} = 18.1, H-4'a), 2.67 (dm, 1H, J_{gem} = 10.1, H-8'a), 2.70 (m, 1H, H-5'), 2.98 (m, 1H, H-7'endo), 8.20 (s, 1H, H-8), 8.76 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 29.16 (C-6'), 32.68 (C-5'), 36.38 (C-4'), 39.87 (C-8'), 40.66 (C-7'), 64.83 (C-1'), 126.12 (C-3'), 132.37 (C-5), 133.33 (C-2'), 143.72 (C-8), 151.07 (C-6), 151.42 (C-2), 152.17 (C-4). ESI MS *m/z* (%): 261.1 (100) [M+H]; HRMS ESI ($C_{13}H_{14}N_5Cl$) calculated: 261.09070, found: 261.09200. For $C_{13}H_{13}N_4Cl$ (260.72) calculated: 59.89% C, 5.03% H, 21.49% N, 13.60% Cl; found: 59.59% C, 5.01% H, 21.17% N, 13.90% Cl.



9-[(1*R,5*S**)-bicyclo[3.2.1]oct-2-en-1-yl]-9*H*-purin-6-amine (404)**

Ammonolysis was performed according to method **F1** starting from **403** (100 mg, 0.4 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water - methanol mixture. Yield 73 mg, 79%, white crystals (m.p. = 217°C).

^{1}H NMR (500 MHz, DMSO): δ 1.54 (m, 1H, H-6'endo), 1.95 (dm, 1H, J_{gem} = 17.8, H-4'b), 2.08 - 2.16 (m, 3H, H-6'exo, H-7'exo, H-8'b), 2.41 (dm, 1H, J_{gem} = 18.0, H-4'a), 2.53 (dm, 1H, J_{gem} = 10.2, H-8'a), 2.56 (m, 1H, H-5'), 2.80 (m, 1H, H-7'endo), 5.55 (dm, 1H, $J_{3',2'}$ = 9.6, H-3'), 5.96 (dm, 1H, $J_{2',3'}$ = 9.6, H-2'), 8.11 (s, 1H, H-2), 8.15 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO): δ 29.06 (C-6'), 32.36 (C-5'), 36.22 (C-4'), 39.38 (C-8'), 40.51 (C-7'), 63.44 (C-1'), 119.86 (C-5), 124.82 (C-3'), 134.84 (C-2'), 139.32 (C-8), 150.04 (C-4), 152.25 (C-8), 156.31 (C-6). ESI MS *m/z* (%): 242.3 (100) [M+H], 264.3 (6) [M+Na]; HRMS ESI ($C_{13}H_{16}N_5$) calculated: 242.14002, found: 242.16998. For $C_{13}H_{15}N_5$ (241.29) calculated: 64.71% C, 6.27% H, 29.02% N; found: 64.88% C, 6.31% H, 28.90% N.

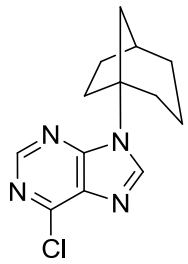


(1*S,2*S**,3*S**,5*S**)-1-(6-chloro-9H-purin-9-yl)bicyclo[3.2.1] octane-2,3-diol (405)**

To a solution of **403** (200 mg, 0.8 mmol) in dioxane - water mixture (4:1, 25 mL) was added NMMO (50 *w* solution in water, 1.5 mL) and OsO_4 (100 μL) and the reaction mixture was stirred at RT for 48 h. Volatiles were evaporated and the crude compound was adsorbed on silica gel and flash chromatographed (85-100% ethyl acetate in hexane)

and subsequently crystallized (toluene - ethyl acetate mixture) to afford **405** (135 mg, 59%) as white needles (m.p. = 199°C).

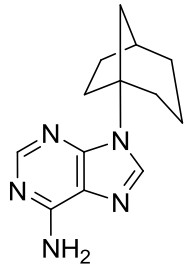
^{1}H NMR (600 MHz, DMSO): 1.45 (m, 1H, H-4ax), 1.57 (m, 1H, H-6endo), 1.63 (m, 1H, H-4eq), 1.84 - 1.90 (m, 2H, H-6exo, H-8b), 1.92 (td, 1H, J_{gem} = $J_{7ex-6ex}$ = 12.7, $J_{7ex-6en}$ = 4.0, H-7exo), 2.31 (m, 1H, H-5), 2.52 (dm, 1H, J_{gem} = 10.3, H-8a), 2.62 (m, 1H, H-7endo), 3.79 (dddd, 1H, J_{3-2ax} = 11.4, J_{3-OH} = 7.3, J_{3-4eq} = 6.0, J_{3-2} = 3.9, H-3), 4.06 (m, 1H, H-2), 4.42 (d, 1H, J_{OH-3} = 7.4, OH-3), 4.80 (d, 1H, J_{OH-2} = 4.4, OH-2), 8.56 (s, 1H, H-8'), 8.74 (s, 1H, H-2'). ^{13}C NMR (150 MHz, DMSO): 27.21 (C-6), 31.81 (C-5), 32.32 (C-7), 35.41 (C-8), 36.05 (C-4), 65.37 (C-3), 126.12 (C-3'), 69.46 (C-1), 73.18 (C-2), 131.76 (C-5'), 147.27 (C-8'), 149.08 (C-6'), 151.00 (C-2'), 152.14 (C-4'). ESI MS *m/z* (%): 295.2 (11) [M+H], 317.2 (100) [M+Na]; HRMS ESI ($C_{13}H_{16}N_4O_2Cl$) calculated: 295.09563, found: 295.09565. For $C_{13}H_{15}N_4ClO_2$ (294.74) calculated: 52.98% C, 5.13% H, 19.01% N, 12.03% Cl; found: 53.16% C, 5.15% H, 18.65% N, 12.02% Cl.



9-[(1*R,5*S**)-Bicyclo[3.2.1]oct-1-yl]-6-chloro-9*H*-purine (406)**

6-Chloropurine nucleobase was constructed according to method **C1** (317 mg, 2 mmol of **402**, *n*-BuOH as a solvent, 160°C for 4h in MW reactor. Mobile phase: 20-40% ethyl acetate in hexane. Crystallization from cyclohexane - pentane mixture. Yield 191 mg, 37% as white ctystals (m.p. = 144.8 - 145.8˚C).

^{1}H NMR (500 MHz, DMSO): δ 1.55 (m, 1H, H-4'b), 1.60 (m, 1H, H-4'a), 1,68 (m, 3H, H-6'endo), 1.75 - 1.87 (m, 3H, H-2'b, H-3'), 2.02 - 2.13 (m, 2H, H-6'exo, H-7'exo), 2.25 - 2.33 (m, 3H, H-2'a, H-8'), 2.55 (m, 1H, H-5'), 2.69 (m, 1H, H-7'endo), 8.15 (s, 1H, H-8), 8.72 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): δ 19.59 (C-3'), 27.81 (C-6'), 31.06 (C-4'), 34.47 (C-7'), 34.83 (C-5'), 38.53 (C-2'), 43.40 (C-8'), 66.17 (C-1'), 132.34 (C-5), 143.47 (C-8), 150.97(C-6),151.13 (C-2), 151.97 (C-4). HRMS ESI ($C_{13}H_{16}N_4Cl$) calculated: 263.10580, found: 263.10580. For $C_{13}H_{15}ClN_4$ (262.74) calculated: 59.43% C, 5.75% H,13.49%Cl, 21.32% N; found: 59.57% C, 5.81% H, 13.25%Cl, 21.15% N.



9-[(1*R,5*S**)-bicyclo[3.2.1]oct-1-yl]-9*H*-purin-6-amine (407)**

Ammonolysis was performed according to method **F1** starting from **406** (100 mg, 0.38 mmol). Mobile phase: ethyl acetate - acetone - ethanol - water 100:15:6:4. Crystallization from water - methanol mixture. Yield 40 mg, 43%, white crystals (m.p. = 247-248°C).

^{1}H NMR (500 MHz, DMSO): δ 1.48-1.60 (m, 2H, H-4'), 1.64 (m, 1H, H-6'endo), 1,72-1.83 (m, 3H, H-2'b, H-3'), 1.98-2.11 (m, 2H, H-6'exo, H-7'exo), 2.21 (dm, 1H, J_{gem}= 10.3, H-8'b), 2.25-2.31 (m, 2H, H-2'a,H-8'a), 2.51(m, 1H, H-5'), 2.65 (m, 1H, H-7'endo), 6.00 (m, 2H, NH_2), 7.85 (s, 1H, H-8), 8.33 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, DMSO): δ 19.64 (C-3'), 27.88 (C-6'), 31.16 (C-4'), 34.52 (C-7'), 34.84 (C-5'), 38.63 (C-2'), 43.48 (C-8'), 65.36 (C-1'), 120.50 (C-5), 138.89 (C-8), 150.27 (C-4), 151.48 (C-2), 155.25 (C-6). HRMS ESI ($C_{13}H_{18}N_5$) calculated: 244.15567, found: 244.15570. For $C_{13}H_{17}N_5$ (243.31) calculated: 64.17% C, 7.04% H, 28.78% N; found: 63.93% C, 7.11% H, 28.59% N.

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